Translating Evidence to Practice: Approaches for Individualized and Patient-Centered MS Care

Fred D. Lublin, MD
Saunders Family Professor of Neurology
Director, Corinne Goldsmith Dickinson Center for Multiple Sclerosis
Icahn School of Medicine at Mount Sinai
New York, NY

Fred D. Lublin, MD
Disclosures

- ***Research/Grants:*** Actelion Pharmaceuticals; Biogen; Brainstorm Cell Therapeutics Inc; National Institutes of Health (NIH); National Multiple Sclerosis Society (NMSS); Novartis; Sanofi
- ***Speakers Bureau:*** Sanofi (non-promotional)
- ***Consultant/Advisory Board/DSMB:*** Acorda Therapeutics; Actelion Pharmaceuticals; Apitope; Atara Biotherapeutics, Inc.; Avotres; Biogen; Brainstorm Cell Therapeutics Inc.; EMD Serono, Inc.; GW Pharmaceuticals; Immunic, Inc.; Innate Immunotherapeutics; Jazz Pharmaceuticals, Inc.; Mapi Pharma; MedDay Pharmaceuticals; MedImmune/Viela Bio; Mylan; Novartis; Orion Biotechnology; Polpharma; The Population Council, Inc.; Receptos, Inc./Celgene Corporation; Roche/Genentech, Inc.; Sanofi/Genzyme Corporation; Teva Pharmaceuticals; TG Therapeutics

Learning Objective 1

Evaluate the latest clinical data on the safety and efficacy of current and emerging therapies for MS and Develop a patient centered care plan.

Four Known Types of MS

- Clinically isolated syndrome (CIS)
- Relapsing-remitting MS (RRMS)
  - About 85% of people are diagnosed with RRMS
- Primary progressive MS (PPMS)
  - About 15% of people experience this course
- Secondary progressive MS (SPMS)
  - Most people diagnosed with RRMS will eventually transition to SPMS

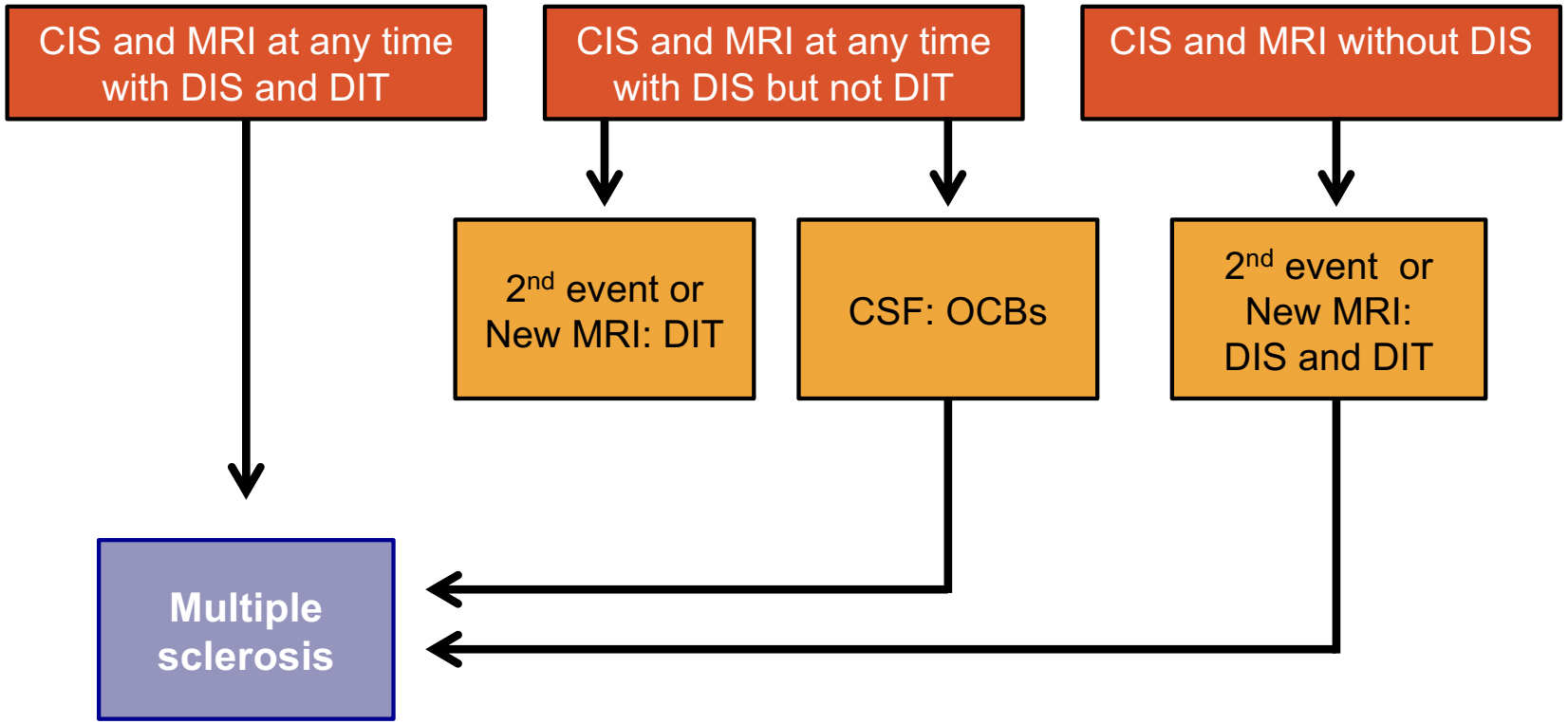
Epidemiology

- Most cases occur between ages 15 and 45; women outnumber men 3:1
- 85% present with relapsing-remitting MS (RRMS)
- The incidence of MS is increasing

Economic and Social Impact

- Prevalence: >450,000 in US and 2.5 million worldwide 1,000,000 in US
- Duration of disease: 30 years
- WHO top 100 diseases; quality of life (QOL)
- 30% severe disability
- 70% unemployed
- High cost of MS drugs
- Lower costs, repurposed approved agents

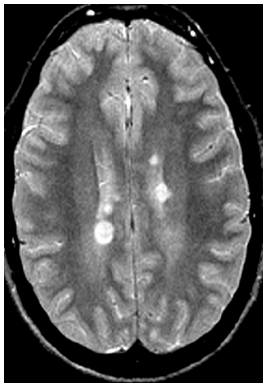
Proposed Diagnostic Algorithm



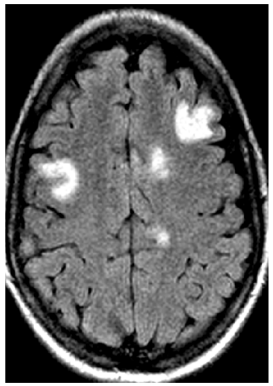
2017 McDonald Criteria for Demonstration of DIS by MRI

DIS: ≥ 1 T2 lesions in ≥ 2 locations

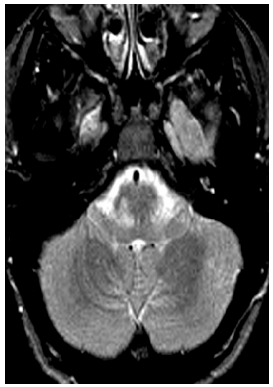
periventricular



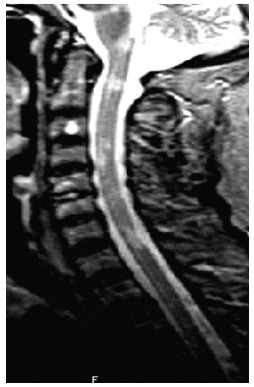
cortical / juxtacortical



infratentorial



spinal cord



Changes from the 2010 McDonald Criteria:

- No distinction between symptomatic and asymptomatic lesions
- Both cortical and juxtacortical lesions can be utilized

Thompson AJ, et al. *Lancet Neurol*. (in press)

Mechanisms of Worsening of MS

- Clinical
  - Incomplete recovery from exacerbations in relapsing forms (step-wise worsening)
  - Gradual, progressive worsening independent of relapses-progressive forms
- Pathological
  - Inflammatory Disease
  - Degeneration

Prognostic Features in Early MS

Better prognosis

- Caucasian
- Monofocal onset
- Onset with optic neuritis or isolated sensory symptoms
- Low relapse rate first 2–5 years
- Long interval to second relapse
- No or low disability at 5 years
- Abnormal MRI
  Low lesion load

Poorer prognosis

- Afro-American or non-white
- Multifocal onset
- Onset with motor, cerebellar, or bladder/bowel symptoms
- High relapse rate first 2–5 years
- Short inter-attack latency
- Disability at 5 years
- Abnormal MRI
  - ≥2 contrast lesions
  - ≥9 T_2 lesions
- + OCB

1. Miller DH, *et al. J Manag Care Pharm* 2004;10:S4–S11.; 2. Kantarci O, *et al.* Prognostic Factors in Multiple Sclerosis. In: *Handbook of Multiple Sclerosis* (3rd ed). Cook SD, editor. New York: Marcel Dekker. 2001. pp 449–463.

Predictors of a Poor Prognosis in MS

Demographic and environmental factors

- Older age
- Male sex
- Not of European descent
- Low vitamin D levels
- Smoking
- Comorbid conditions

Clinical factors

- Primary progressive disease subtype
- A high relapse rate
- A shorter interval between the first and second relapses
- Brainstem, cerebellar or spinal cord onset
- Poor recovery from the first relapse
- A higher Expanded Disability Status Scale score at diagnosis
- Polysymptomatic onset
- Early cognitive deficits

MRI observations

- A high number of T2 lesions
- A high T2 lesion volume
- The presence of gadolinium-enhancing lesions
- The presence of infratentorial lesions
- The presence of spinal cord lesions
- Whole brain atrophy
- Grey matter atrophy

Biomarkers

- A high number of T2 lesions
- The presence of IgG and IgM oligoclonal bands in the CSF
- High levels of neurofilament light chain in the CSF and serum
- High levels of chitinase in the CSF
- Retinal nerve fibre layer thinning detected with optical coherence tomography

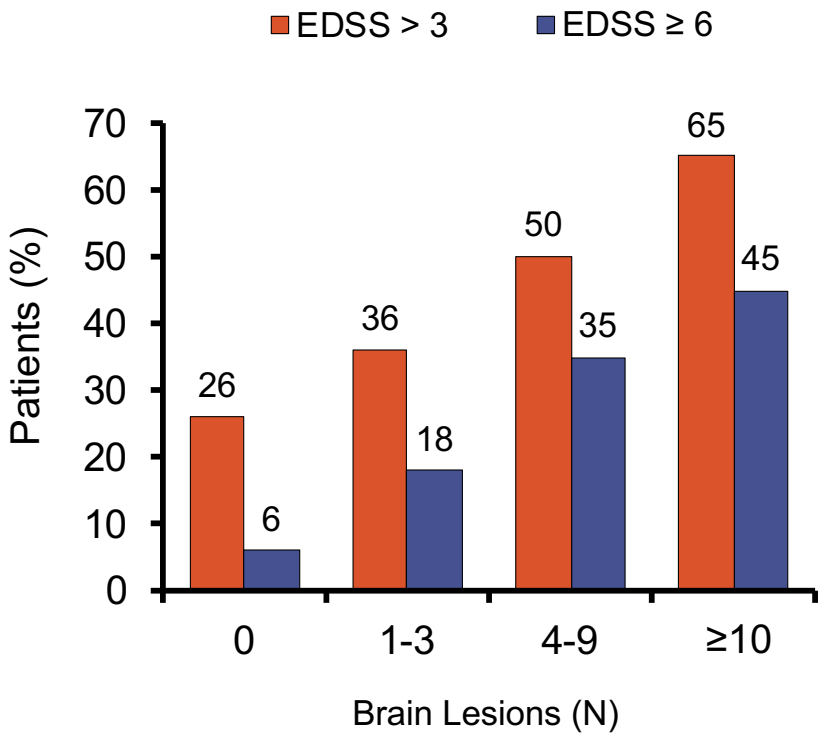
Rotstein D, X Montalban. *Nat Rev Neurol*. 2019;15(5):287-300.

Predicting the Course of MS

- Clinical features of onset bout
  - Motor worse than sensory
  - Polyregional worse than monosymptomatic
  - Early bladder involvement poor prognosis
- Incomplete recovery from initial attack
- Short interval between attacks

Prognosis

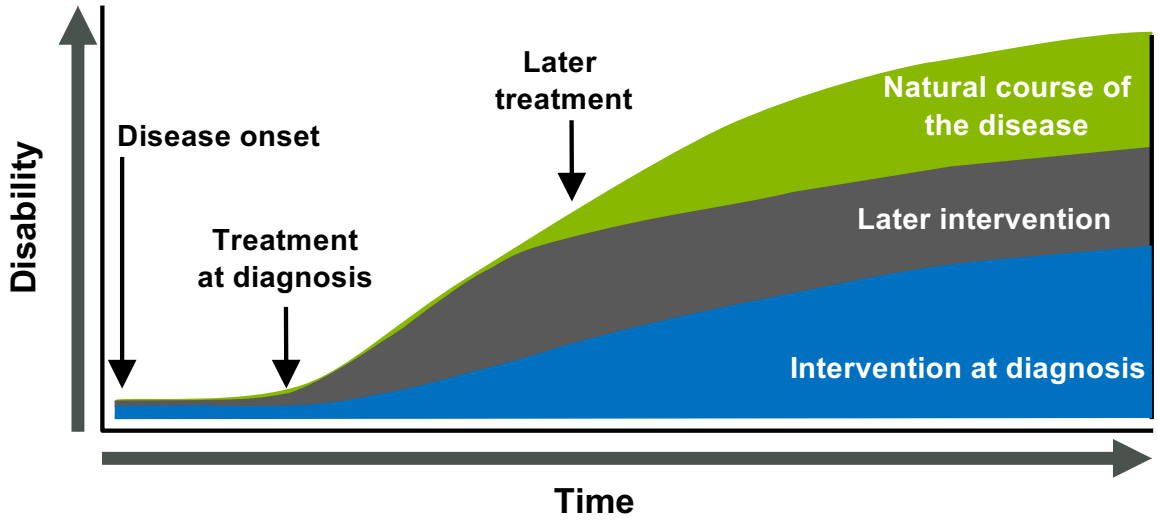
- Initial MRI
  - T2 lesion numbers
  - Median EDSS at 20 years = 6 for >10 T2 lesions
  - 3 or 4 Barkhof criteria moderate correlation with EDSS at 5 years



What is the "Risk" of a Patient for Imminent Disease Worsening?

- What is the impression of the patient's disease to date?
  - Mild, early, typical
  - Moderate or severe accumulated deficits, later disease, more aggressive than normal
- How fast do we want a given treatment to work?
- What "other factors" (e.g. pregnancy, adherence) should be considered?
- But, we lack good prognostic markers

Early Intervention in MS: Maximizing the Use of the Therapeutic Window



- The therapeutic window in MS offers the greatest opportunity for long term benefit
- Finding the most appropriate intervention as early as possible is key

Miller JR. *J Manag Care Pharm* 2004;10(suppl S-b):-11. S4.

Treating Multiple Sclerosis

- Disease modifying Rx
- Rx of acute exacerbations
- Enhanced recovery
- Enhanced function
- Symptomatic Rx
- Neuroprotection
- Repair

Potential Strategies for Use of Disease-Modifying Therapy

- Step Therapy
- Use More Potent Therapy Initially
- Induction Therapy
  - What defines a suitable induction agent?
  - De-escalation?

Treatment Initiation Based on Risk

Induction (High Risk)

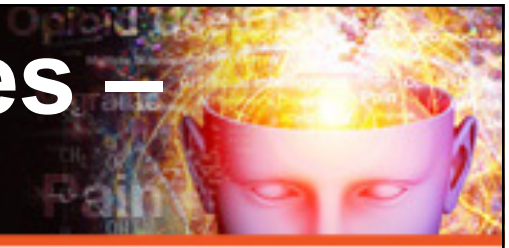
- Start with a higher efficacy agent
  - Obtain a treatment "response" for a given period of time
- Revert back to a 1st line (safer) treatment to maintain efficacy and minimize toxicity

vs.

Escalation (Low Risk)

- Start with a 1st line agent
- Monitor treatment "response"
- If sub-optimal response, move to a higher efficacy agent
- Monitor treatment "response"
- Move to a higher efficacy agent

How Will We Choose Therapies – Clinical



- Natural history versus unnatural history
- Observational studies
- How to compare – statistical inferences
- Who knows where the biases are?
  - Bias beats statistics

How Will We Choose Therapies – Clinical

- Comparative studies: head-to-head: Best
- Tracking Arms: May be underpowered
- Inference: Inaccurate, but common
- Options: Becoming more common

Disease Modifying Medications: Categories

Immunomodulators

Interferon-b
GA
DMF
Teriflunomide

Pros
- Safety
- Long term experience

Cons
- Modest efficacy
- Many injectable

Anti-Cell Trafficking Agents

Fingolimod
Natalizumab
Siponimod
(Ozanimod*)
(Ponesimod*)

Pros
- Greater efficacy
- Onset of action quick
- Well tolerated

Cons
- Opportunistic infections (PML)
- Cells still in body
- Rebound disease
- Long term safety unclear

Cell Depleting Therapies

Alemtuzumab
Cladribine Tablets
Ocrelizumab
Teriflunomide
(Ofatumumab*)
AHSCT (BMT)

Pros
- Definitive in depleting disease causing cells
- Some are IRT
- No rebound disease

Cons
- Opportunistic infections
- Secondary autoimmunity (alemtuzumab)
- Most cumbersome

*Not yet licensed by the FDA in the USA
[Package Insert]. Drugs@FDA Website.

Comparison of Main Outcome Measures in Established Treatments

Study Agent	IFNβ-1b 250μg sc eod	IFNβ-1a 30μg im qw	IFNβ1a 44μg sc tiw	Glatiramer Acetate 20mg sc od
Relative Reduction in ARR	34%	18%	32%	29%
Absolute Reduction in ARR	0.43	0.15	0.41	0.4
Relative Reduction in new T2 & Gd+ MRI Activity	83%	52%	78%	30%
Relative Reduction in EDSS Progression	39%*	37%	30%	12%*
Absolute Reduction in Proportion Progressing	8%*	13%	11%	3%*

*p = ns

IFNB Study Group Neurol 1993; 43(4):655–61.; Jacobs LD, et al *Ann Neurol* 1996;39(3):285-289.; PRISMS Study Group. *Lancet* 1998;352(9139):1498–504.; Johnson KP, et al. Neurology 1995;45(7):1268–1276.

Comparison of Main Outcome Measures in Recent Treatments

Study Agent	Natalizumab	Fingolimod	Teriflunomide	DMF
Relative Reduction in ARR	68%	54%	31%	53%
Absolute Reduction in ARR	0.5	0.22	0.17	0.19
Relative Reduction in new T2 & Gd+ MRI Activity	83%[6] 92%	74% 82%	67%	85%[7] 90%
Relative Reduction in EDSS Progression	42%	30%	30%	38%
Absolute Reduction in Proportion Progressing	12%	6.4%	7.1%	10.7%

Yearly scan only. 7. ~43% of pts scanned, scans; only 3 scans performed

Polman CH, et al. *N Engl J Med* 2006;354:899–910.; Kappos L, et al. N Engl J Med 2010;362:387-401.; O' Connor P. et al. N Engl J Med 2011;365:1293-1303.; Data from bid dosing.; Comi AAN 2011 presentation.

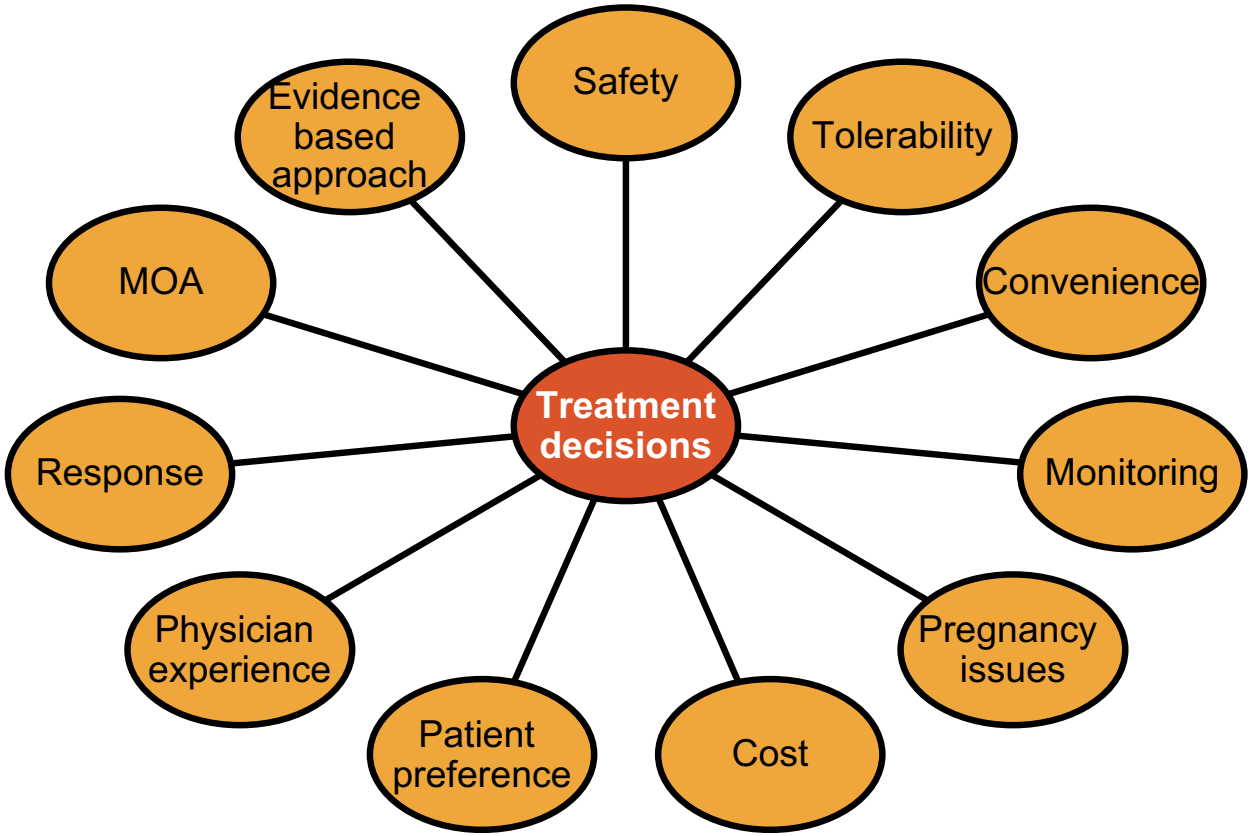
What to Follow?

- Adherence – is the drug tolerated?
  - Managing side effects
  - Laboratory monitoring
- Disease activity
  - Relapse:
    - Quality, quantity, recovery
  - Progression
    - EDSS, MSFC, cognition
  - MRI

“Personalizing” Treatment for MS

- Start early with the most effective treatment appropriate to the “window of presentation”
  - Future biomarkers may allow for more precise personalized DMD selection
- Have a plan to determine “sub-optimal responders” after a reasonable time on first therapy and an approach to switching or ‘escalating’ therapy
- Consider more aggressive starting therapy for patients with either silent advanced disease or early signs of poor prognosis

Making Treatment Decisions Considering the Benefits and Risks



Comparative Efficacy

- High dose/frequency IFN vs. low dose/frequency IFN
- High dose/frequency IFN vs. GA
- Low dose/frequency IFN vs. GA
- Low dose/frequency IFN vs. fingolimod
- High dose/frequency IFN vs. teriflunomide
- High dose/frequency IFN vs. alemtuzumab
- High dose/frequency IFN vs. ocrelizumab
- Low dose/frequency IFN vs. daclizumab

So, Where Are We?

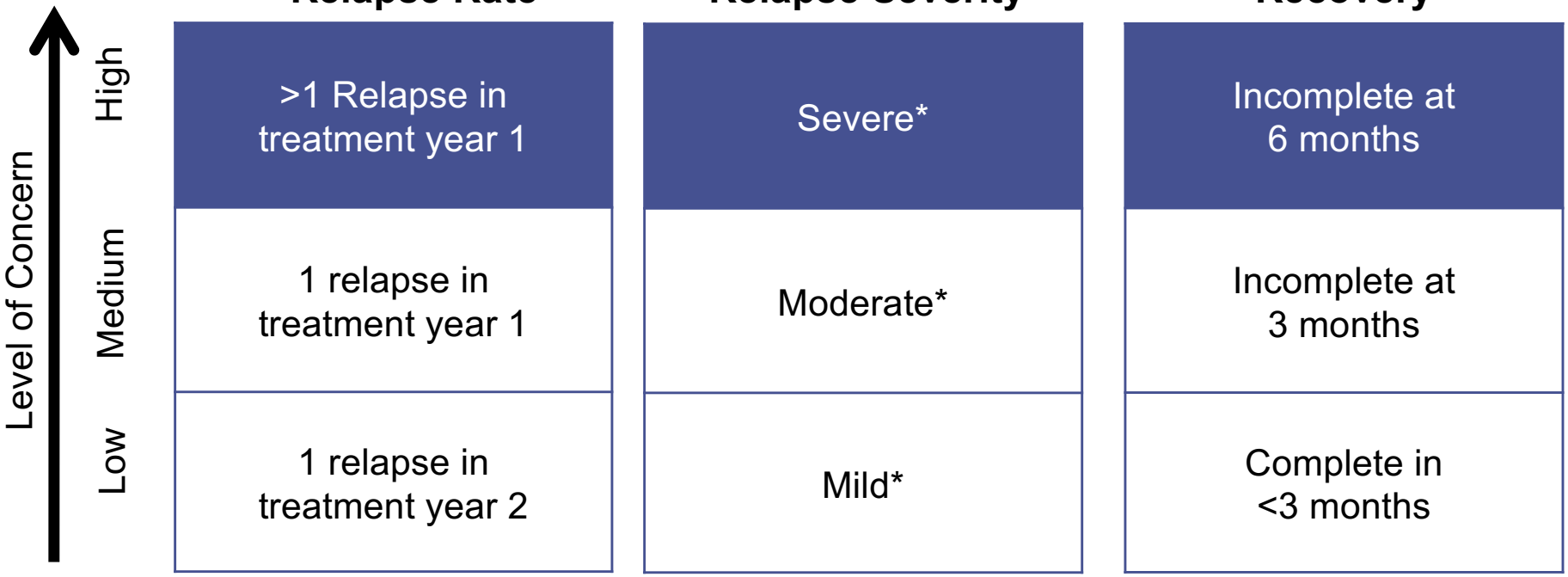
- We do not yet have the tools to confidently predict individual treatment response
- We have an idea of how groups of patients perform
- We need more head-to-head comparative studies
- We need longer term data of safety and efficacy
- We need biomarkers of treatment response

A Modern Proactive Approach to MS Disease Modifying Therapy

- Setting a higher standard of success for:
  - Prevention of Relapses
  - Prevention of MRI changes
  - Prevention of Disability
- Emerging concept of the disease activity free state (NEDA)

Monitoring MS: Treatment Response

Relapse-based Assessments



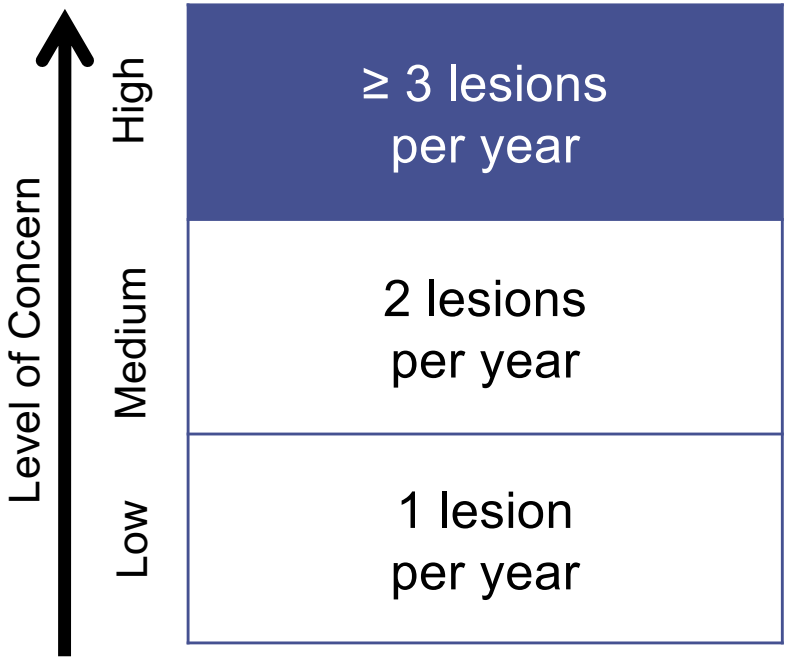
*Severity measured by need for steroids, need for hospitalization, effect on activities of daily living, number of functional domains affected, and degree of motor/cerebellar involvement.

Freedman MS, et al. *Can J Neurol Sci.* 2013;40:307-323.

Monitoring MS: Treatment Response

MRI-based Assessments

New T2 or Gd Lesions*



*MRI follow-up with Gd enhancement is recommended 6–12 months after starting MS therapy.

Freedman MS, et al. *Can J Neurol Sci.* 2013;40:307-323.

Monitoring MS: Treatment Response

Disability-based Assessments

Level of Concern	EDSS ≤ 3.5*	EDSS 4.0–5.0*	EDSS ≥ 5.5*	Clinical Progression	T25FW
High	>2 points at 6 mo; 2 points at 12 mo	>1 points at 6 mo; 1 point at 12 mo	>0.5 points at 6 mo	Pronounced motor, cerebellar, or cognitive; multiple EDSS domains	≥100% confirmed at 6 mo
Medium	2 points at 6 mo	1 point at 6 mo	0.5 points at 6 mo	Some motor, cerebellar, or cognitive; multiple EDSS domains	>20% to <100% confirmed at 6 mo
Low	≤1 point	<1 point	-	No motor; minor sensory	≤20% confirmed at 6 mo

Abbreviations: EDSS, Expanded Disability Status Scale; T25FW, Timed 25-Foot Walk Test.

Freedman MS, et al. *Can J Neurol Sci*. 2013;40:307-323.

Ultimately the Patient Must Choose

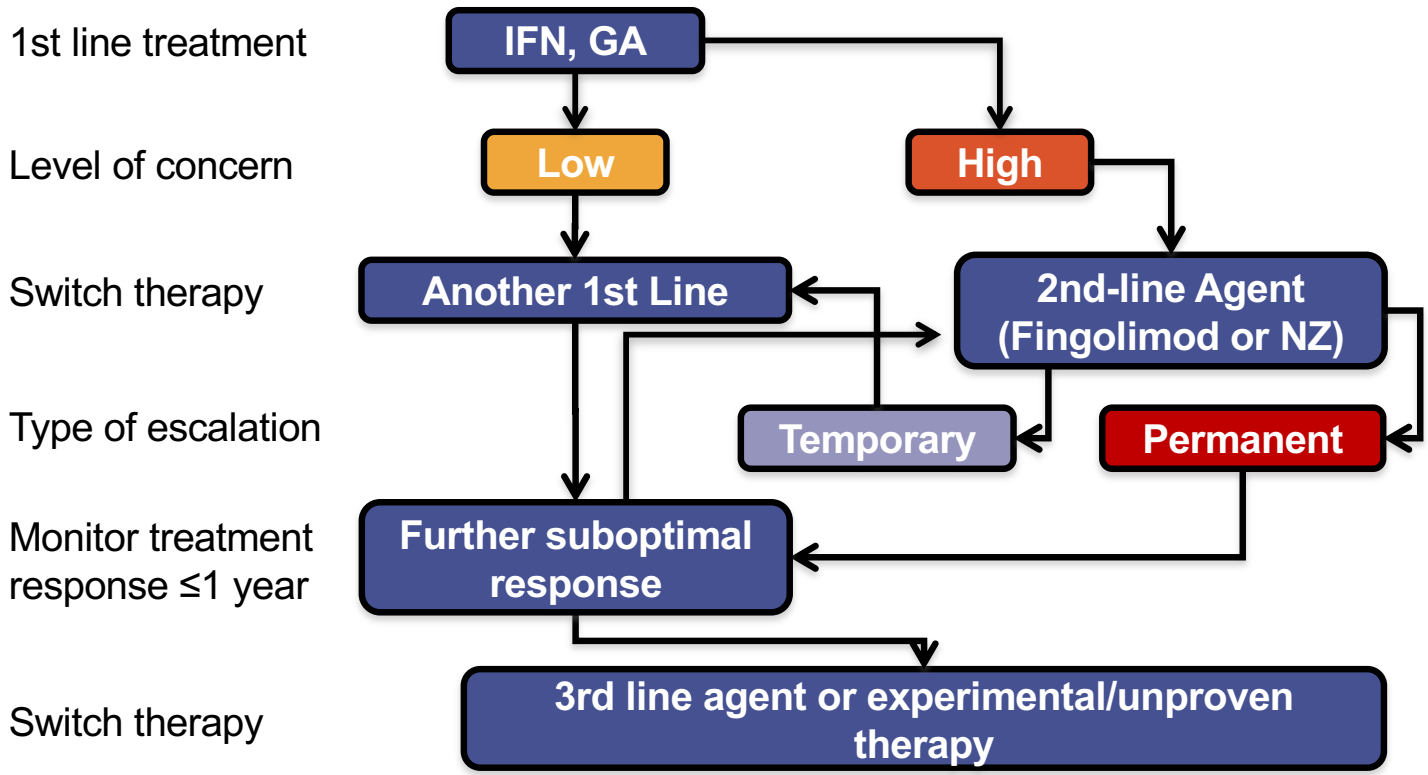
Patient-related considerations

- Occupation
- Lifestyle
- Travel
- Vaccinations
- Monitoring availability
- Pregnancy
- Ability to use various formulations (ie, fear of injections)

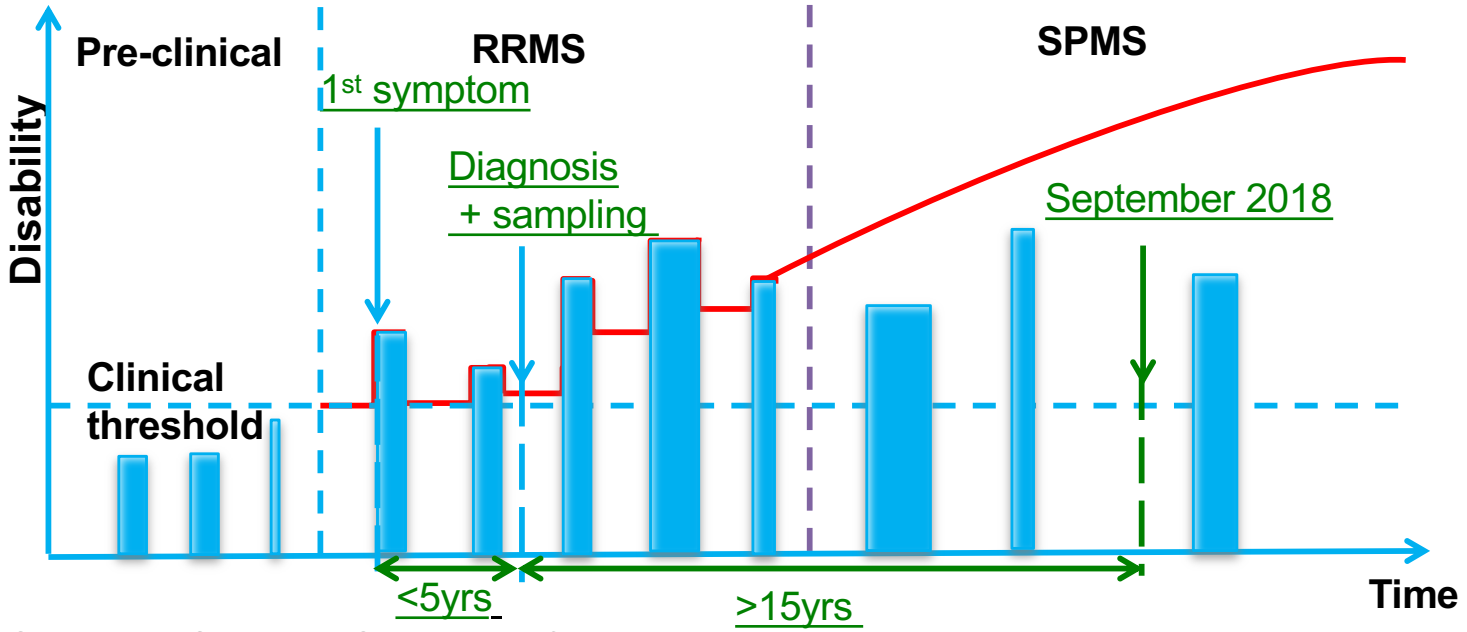
Medication-related considerations

- Adverse events
- Risk vs benefit
- Treatment goals
- Severity of disease

Switching Therapy



Is Baseline Serum NfL a Marker of MS Future Disability?



Screened Ottawa MS bio bank for serum:

- Collected < 5 years from first MS symptom (usually at the time of diagnosis)
- > 15 years of follow-up post sampling at Ottawa MS clinic
- **67 patients** : Mean follow-up: 15.8 years after sampling (Max:23.7, Min 10.52)
- **40 non-inflammatory controls**

Thebault S, et al. *Ann Clin Trans Neurol*. (manuscript submitted)

Symptomatic Issues in MS

- Spasticity
- Spasms
- Dystonia
- Bladder dysfunction
- Bowel dysfunction
- Sexual dysfunction
- Fatigue
- Tremor
- Psychiatric disorders
- Psychological disorders
- Pain
- Skin care
- Speech/swallow dysfunction
- Complications of Rx

SMART Goals

Specific, Measurable, Attainable, Relevant, Timely

- Early intervention in patients with MS offers the greatest opportunity for long-term benefit
- Consider benefit and risk profile of treatment, taking into consideration patient preferences

Mount Sinai

The Corinne Goldsmith Dickinson Center for MS

Thank You

Questions & Answers

Don’t forget to fill out your evaluations to collect your credit.