actrims FORUM 2024

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BREAKING BARRIERS IN MS

Industry Supported Satellite Symposium Disclosure

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New Frontiers in Optimizing Patient Outcomes in Multiple Sclerosis:

Strategies for Early Intervention to Address Progression Independent of Relapse

Welcome and Introductions

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Disclosures

Stephen Krieger, MD, FAAN

Consulting Fees: Baim Institute, Biogen, Cycle, EMD Serono, Genentech, Novartis, Octave, Genzyme/Sanofi, and TG Therapeutics

Research: Biogen, BMS, Novartis, Sanofi

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Consulting Fees: Alexion, EMD Serono, Genentech, Horizon, Sanofi

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Case #1:
How Stable is Stable?

Stephen Krieger, MD, FAAN
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Global Neurology Academy

Case 1: History

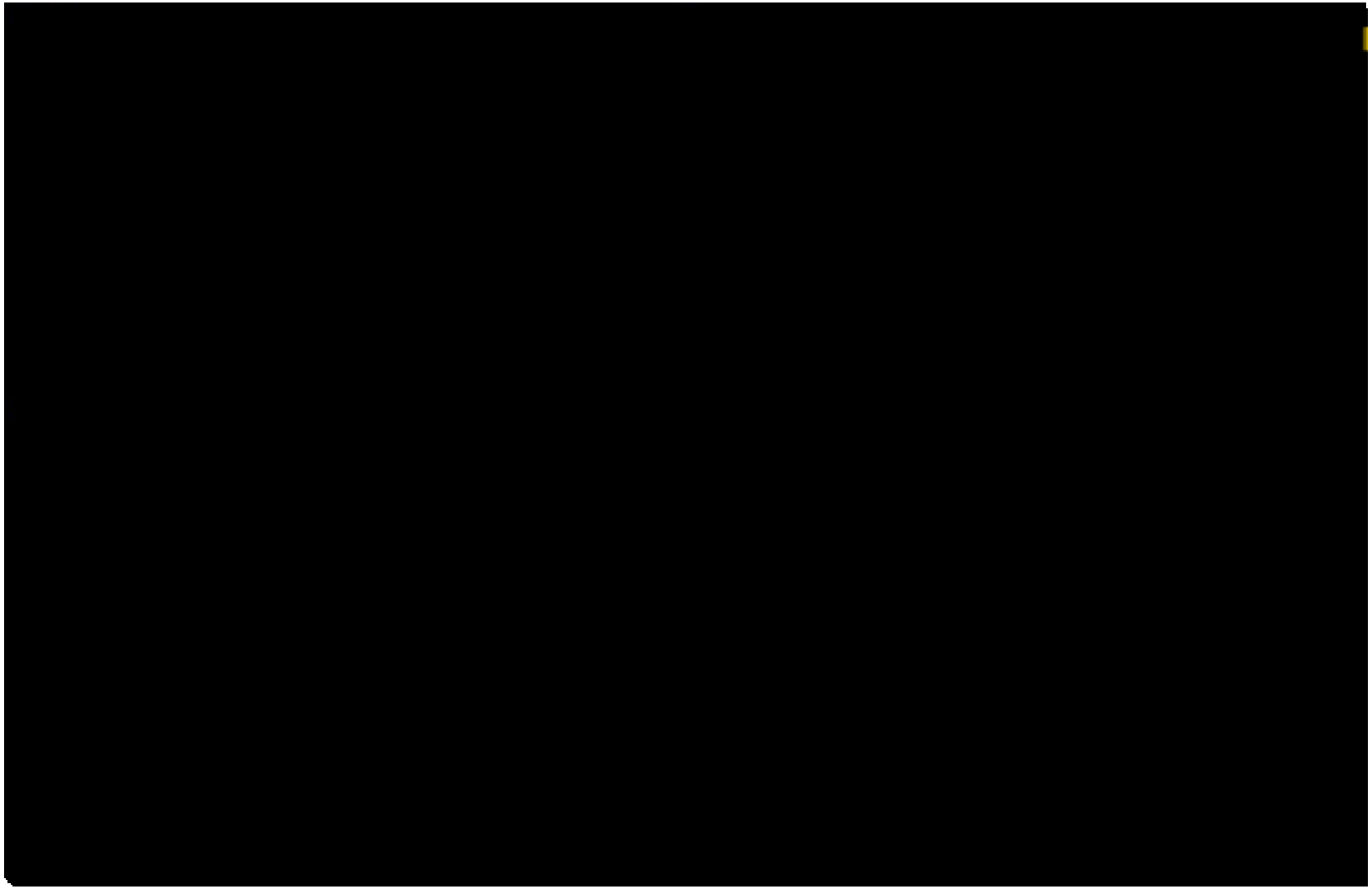
- In 2005 at age 24, while in an MBA program, she noted numbness in her feet when biking or working out, would resolve in minutes to hours but some persistent L foot numbness.
- In 2008 at age 29, developed significant fatigue, needing naps – “my boyfriend thought I had narcolepsy” – saw neurology but no diagnosis made.
- In 2009 at age 30, developed numbness and tingling on L hemibody – arm and leg – lasting for weeks, had MRIs which found lesions, CSF positive for 10 OCBs, and she was diagnosed with MS and started on glatiramer acetate.
- She took modafinil for fatigue but experienced mood disarray, was irritable, crying, and discontinued this; her fatigue slowly resolved with optimizing sleep.

Case 1: History (continued)

- She came to my practice in 2011, and initial neurologic exam was normal with suggestion of trace L foot sensory loss only.

- Interval MRIs were stable for the next 10 years, during which time she remained on GA except during her pregnancies; she delivered two children and was promoted to increasingly senior positions in medical marketing, and she had no relapses.

Case 1: MRI – 2010 Through 2019: (No New Lesions)



Questions for the Panel: Considering Stable MS

- How do we define success in treating RRMS?
- Is this NEDA? Is NEDA always achievable?
- Do you change a lower-efficacy DMT when the treatment goal is being achieved?

Case 1: History (continued)

- She began to complain of worsening fatigue – “Like it was 10 years ago” – and sense of being cognitively overwhelmed at work.

- Neurological exam remained essentially unrevealing, with normal mental status, bright affect, positive, motivated approach, no overt physical or cognitive deficits.

Questions for the Panel: Considering Stable MS

- How would you pursue these symptoms on history-taking?
- What else would you ask her?
  - (My favorite question: “Have you had your annual performance review at work?”)
- How would you further assess her?
- Any specific tests/studies/assessments?

Case 1: Neuropsychology/Cognitive Eval (Summer 2019)

Relevant History:

Ms. _____ reported that she **forgets familiar people's names** (i.e., co-workers), …. This typically happens when she is rushing or when she is hot. … **Still, it has resulted in her feeling embarrassed.** She also noted **some difficulty with cognitive flexibility while focusing** (e.g., responding to questions unrelated to the current conversation …. She described her mood as "good," but **noted feeling more fatigued.**

Baseline Estimation:

Based on educational/occupational attainment and literacy (WTAR raw = 44, estimated VCI at **79th percentile**), estimated **premorbid intellectual function is high**.

Case 1: Neuropsychology/Cognitive Eval (Summer 2019)

High-Sensitivity Cognitive Screener: Average

*The **SDMT (28th percentile)** is a high sensitivity cognitive screener requiring coordination of multiple cognitive functions (e.g., sustained attention, information processing, learning, and lexical retrieval).*

Auditory Attention / Mental Control & Processing Speed: Average

***Information processing speed** was average when asked to rapidly make judgments about images (WAIS-IV Symbol Search **34th percentile**; Decision Speed **18th percentile**).*

Problem Solving: Below Expectations

***Planning / problem solving** was below expectations on a task requiring generation and execution of an efficient strategy to reach a target configuration (Tower of London 2nd Edition: **1st percentile**).*

Case 1: Neuropsychology/Cognitive Eval (Summer 2019)

Language Functions: Average except for low phonemic fluency

*Rapid **word generation was very low** with a phonemic cue (**1st percentile**).*

Memory: Mostly Average except for weak initial verbal learning

Initial learning** of a 12-item word list was well below average; **Total Learning, 6th percentile;

Upper Extremity Function: Below Average Coordination on the Right

Upper extremity coordination** (Nine Hole Peg Test) was below average on the **dominant right (7th percentile)

Gait & Balance: Average

***Tandem walking was normal** (12/12 quarters successfully walked across three trials).*

Case 1: Questions for the Panel

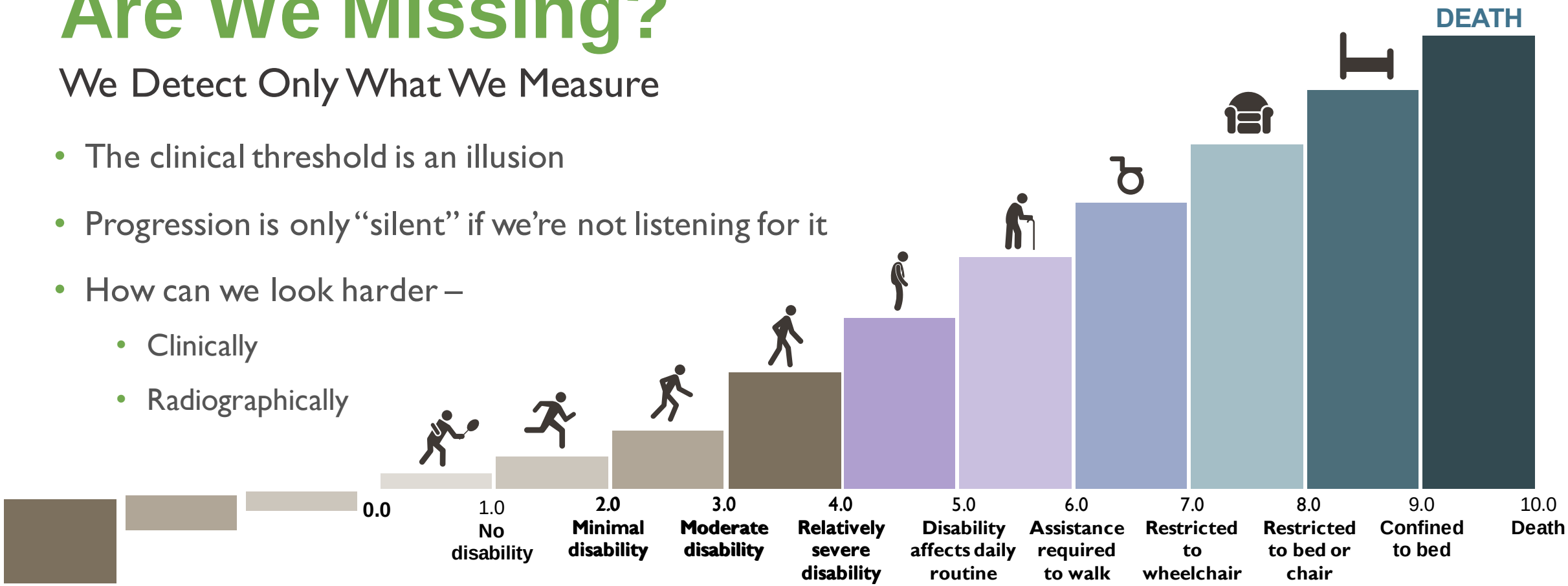
This was a humbling case for me because it showed me what I'd been missing. She had developed cognitive issues, fatigue, loss of stamina insidiously: should we consider this PIRA even in the absence of EDSS changes?

- How do you now consider her burden of disease? Still mild?
- Considering she's a high-functioning professional and mother of 2, are there concerns for her trajectory in the years to come?
- Implications for her treatment strategy or continue glatiramer acetate?

Identifying Progression in MS: What Are We Missing?

We Detect Only What We Measure

- The clinical threshold is an illusion
- Progression is only "silent" if we're not listening for it
- How can we look harder –
  - Clinically
  - Radiographically



1. Confavreux C, Vukusic S. *Brain*. 2006;129:606-616. 2. Kurtzke JF. *Neurology*. 1983;33:1444-1452.
3. Rudick RA, et al. *Arch Neurol*. 2010;67:1329-1335.

MULTIPLE SCLEROSIS JOURNAL | MSJ

Short Report

EDSS 0 is not normal: Multiple sclerosis disease burden below the clinical threshold

Challenging tasks may be a more sensitive measure of sub-threshold deficits that are missed by standard neurological physical exam

EDSS Functional Systems

Cerebral/Cognition

Pyramidal/Motor

Balance/Coordination

Consider Cognition:

$$V_{\mathrm{xc}\,\sigma}(\mathbf{r}) = \sum_i \left(\frac{n_{i\sigma}}{n_\sigma}\right)\left[v_{i\sigma} + \left(\overline{V}_{\mathrm{xc}\,\sigma i} - \overline{v}_{i\sigma}\right)\right] \quad (1)$$

where

$$v_{i\sigma}(\boldsymbol{r}) \equiv \frac{\delta E_{\mathrm{xc}}[\{\phi_{i\sigma}\}]}{f_{i\sigma}\,\phi^*_{i\sigma}(\boldsymbol{r})\,\delta\phi_{i\sigma}(\boldsymbol{r})}, \qquad (f_{i\sigma} \neq 0) \quad (2)$$

Krieger et al, *Int. J. Quantum Chemistry*. 1995

Consider the Pyramidal/Motor Functional System:

S. Krieger, J. Sumowski | EDSS 0 is not Normal, MSJ 2022

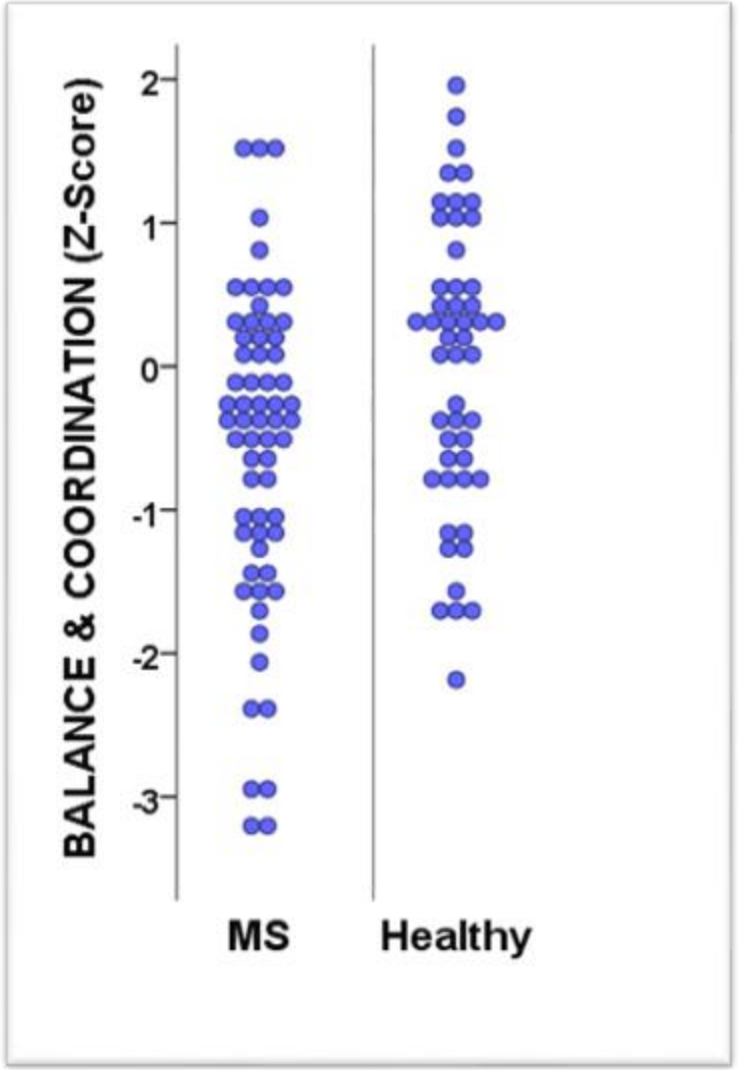
Consider Fine Motor Assessments:

S. Krieger, J. Sumowski | EDSS 0 is not Normal, MSJ 2022

Results: Clinical Findings Using Challenge Tasks

- **MS patients with an EDSS of 0** had normal T25FWs (median 3.95; interquartile range 3.75-4.24)

- **Using a set of challenging tasks:** Patients with EDSS 0 performed worse than controls on upper extremity (t[111] = 2.09, *P* = 0.039, d = 0.39), balance (t[111] = 2.90, *P* = 0.005, d = 0.55), and overall function (t[111] = 2.82, *P* = 0.006, d = 0.54).



Considering Early Progression in MS: A Provocative Question

Contemporary Challenges in the Recognition, Diagnosis, and Management of Progressive Multiple Sclerosis

The challenges associated with identifying the transition to secondary progressive MS are many.

Jasmin Patel, MD, Jamie Nichols, MD, and Stephen Krieger, MD, FAAN

As a thought experiment, if one defines SPMS as predicated on the insidious development of disability, and cognitive dysfunction essentially always manifests gradually, should every person with RIS, CIS, or RRMS with cognitive dysfunction be classified as having SPMS?

Case 1: Conclusion (2019-2023)

- The patient and I were both alarmed by her cognitive profile, though she found it validated many of her long-standing symptomatic concerns.
- We decided to use this as an opportunity to change her DMT strategy and selected an Anti-CD20 agent in the Fall of 2019.
- As of 2023, she has felt cognitively clearer than in the past, and her subsequent neuropsych profiles reflected this improvement.
- She has also optimized her fitness regimen, lost a significant amount of weight, and after certain accommodations were made by her workplace (minimizing distractions & interruptions, allowing continued work from home certain days, etc.) she was promoted yet again.

Addressing Early Progression in MS: Therapeutic Implications

- The best way to treat MS progression is to prevent it
  - High efficacy DMT in early MS, when progressive pathology begins

- While we await clinical trials of restorative therapies: boost reserve and “fill the tank”
  - Exercise regimen
  - PT/OT/Speech therapy
  - Psychotherapy for depression, anxiety, social isolation
  - Diet/metabolism/glucose/body mass index management
  - Cardiovascular risk factor mitigation
  - Smoking cessation
  - Perhaps also dalfampridine

Thank You!

Case #2: Aging in Multiple Sclerosis

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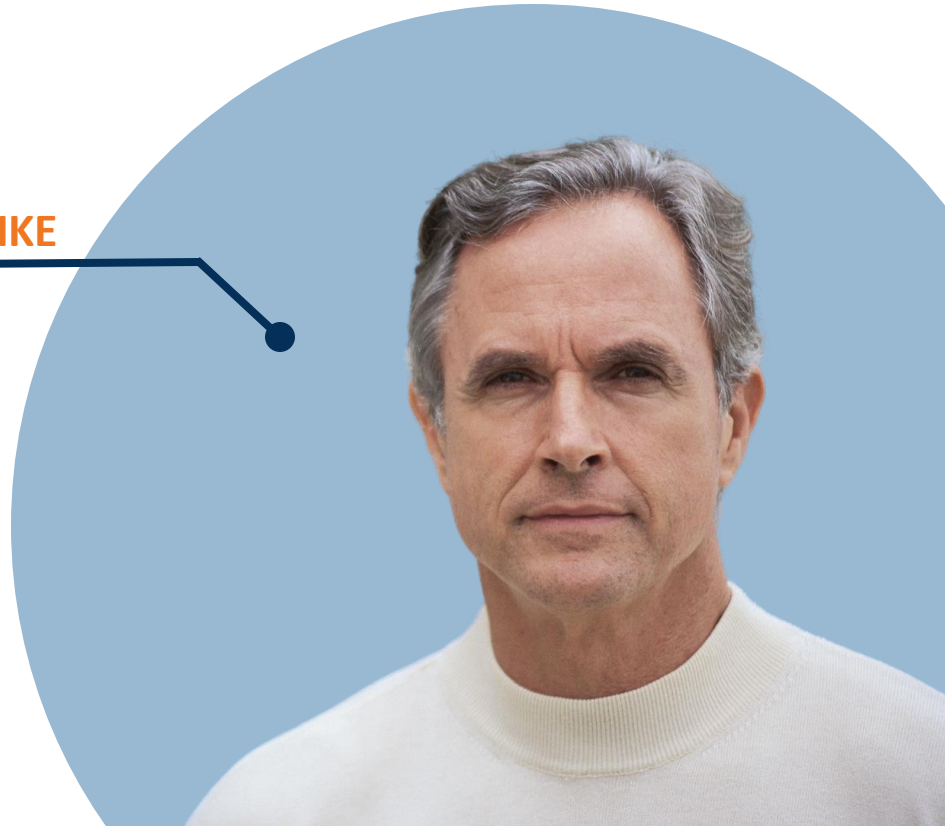
Global Neurology Academy

Case 2: History

- Mike is a 62 yo man, diagnosed with MS at age 35, initial relapsing course
- Currently on ocrelizumab since 2015 after having a transverse myelitis while receiving interferon beta-1a
- EDSS of 3.5 (moderate disability) mostly residual deficits from his last relapse
- He started experiencing more consistent daytime somnolence as regular nocturnal episodes of urinary frequency and urgency occurred for the last 12 months
- He was hospitalized in 2022 due to complications of COVID-19 infection
- His neurological examination and MRI are unchanged



What is the best next step in Mike's care?

- Continue ocrelizumab as his MS is stable and advise him to start modafinil for daytime somnolence
- Continue ocrelizumab and explain that his symptoms are due to smoldering inflammation and current DMTs are ineffective in preventing progression
- Order blood work, UA, and bladder US
- Discontinue ocrelizumab and don't start any other DMTs as his MS is going through immunosenescence

Question for the Panel: What strategies do you implement to mitigate possible infections?

- How do you screen for possible infections/complications of therapy?
- Do you change to a safer DMT when infections become an issue?

Aging and MS
Pathological Processes

Aging and MS

Definitions

Chronological Age

Age defined by birth date

Biological Age

Functional decline and loss of homeostasis over time, influenced by lifestyle

Senescence

State of cells in which they can't replicate but they can produce and secrete proinflammatory molecules

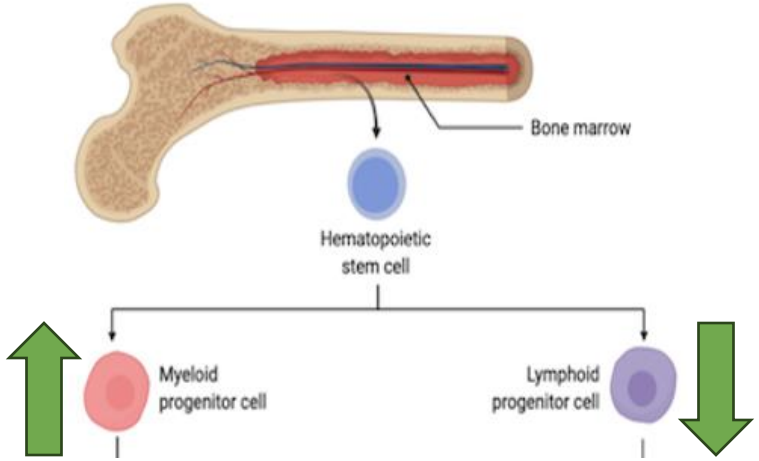
Consequences

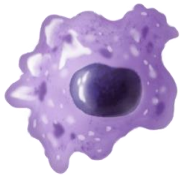
- Weakened antimicrobial immunity
- Increased susceptibility to respiratory infections
- Reactivation of chronic viral infections (e.g., shingles)
- Impaired antivaccine responses
- Insufficient protection against malignancies

Graves JS, et al. *Lancet Neurol*. 2023;22(1):66-77.

Age Alters the Innate and Adaptive Immune Systems

Innate Immune System

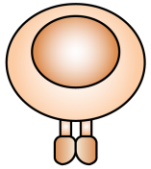




Macrophage

- Phagocytosis
- Cytokine response
- Antimicrobial activity

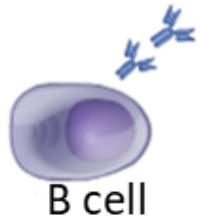
Adaptive Immune System



T cell

- TCR diversity
- Naïve cells
- CD8 frequency

- Proinflammatory responses
- Memory cells



B cell

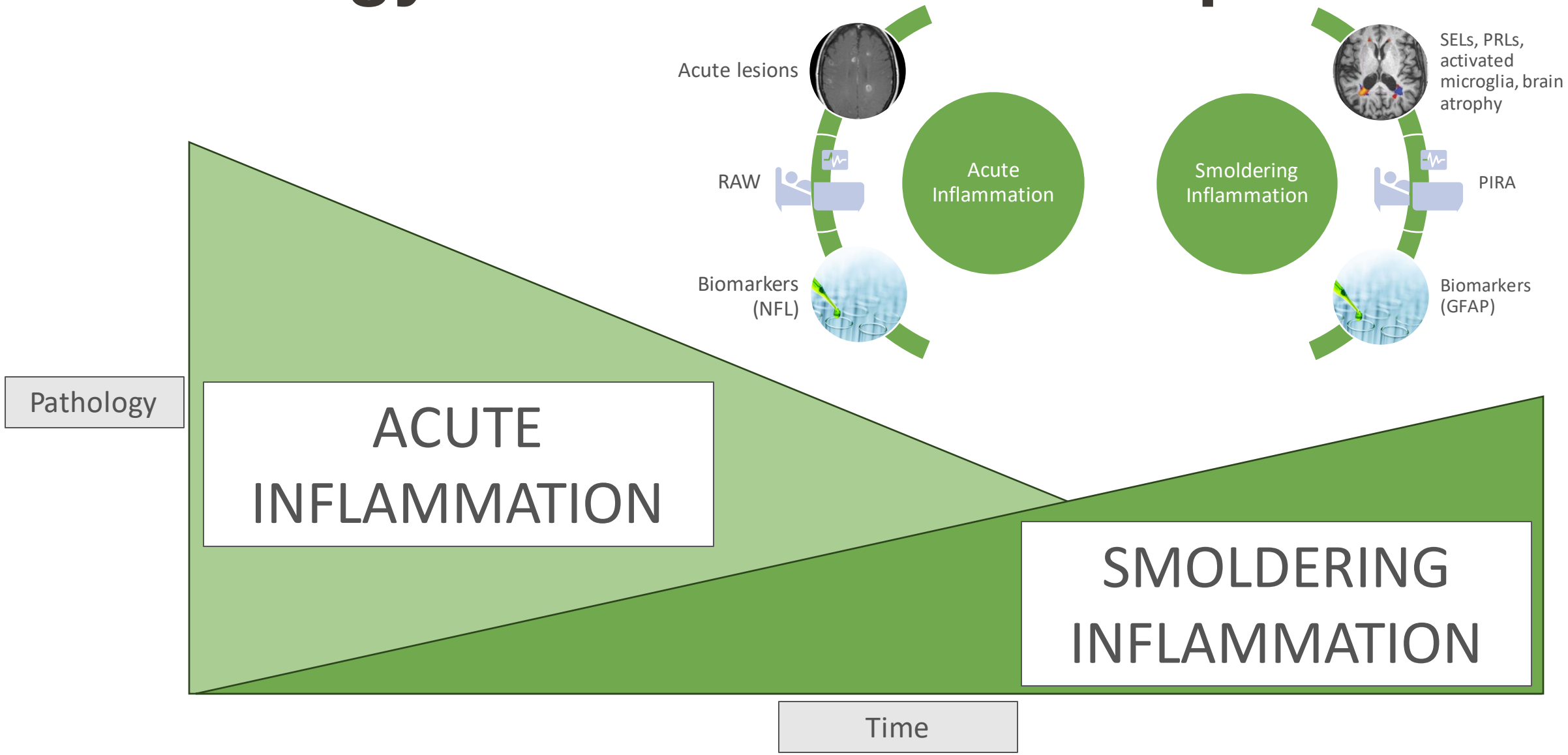
- BCR diversity
- Affinity of Ab
- Neutralizing function Ab

- Proinflammatory responses
- Autoantibodies
- Age associated cells

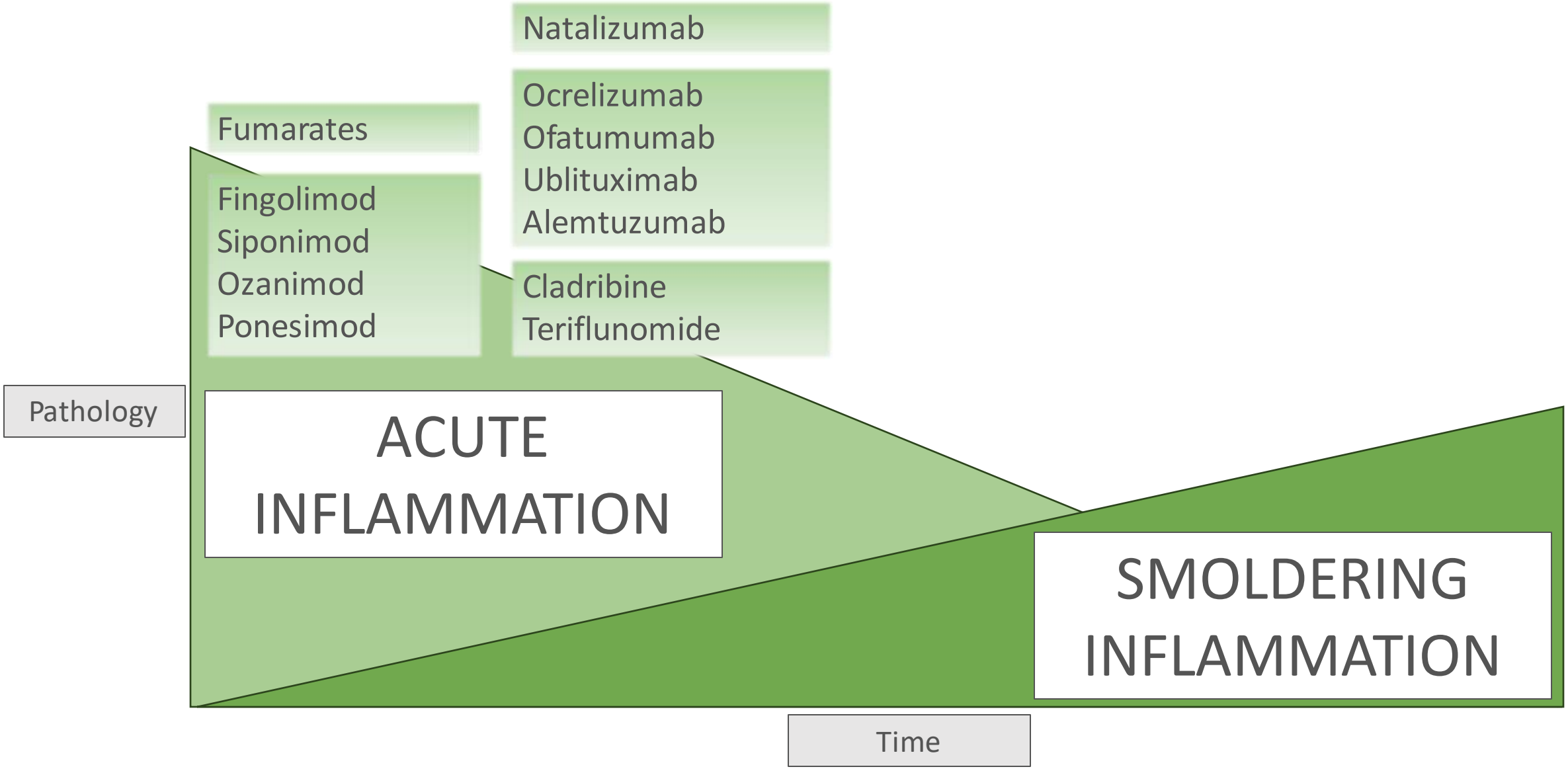
Macaron G, et al. *Front Neurol*. 2023;14:1197212.
Lewis ED, et al. *Prog Neuropsychopharmacol Biol Psychiatry.* 2022;118:110576
Mouat IC, et al. *Cell Mol Life Sci.* 2022;79(8):402.

Clinico-Pathological Correlates in MS

Pathology of MS Over the Lifespan



Effect of DMTs in the Disease Process



How Does Immunosenescence Affect Efficacy/Safety of Current DMTs?

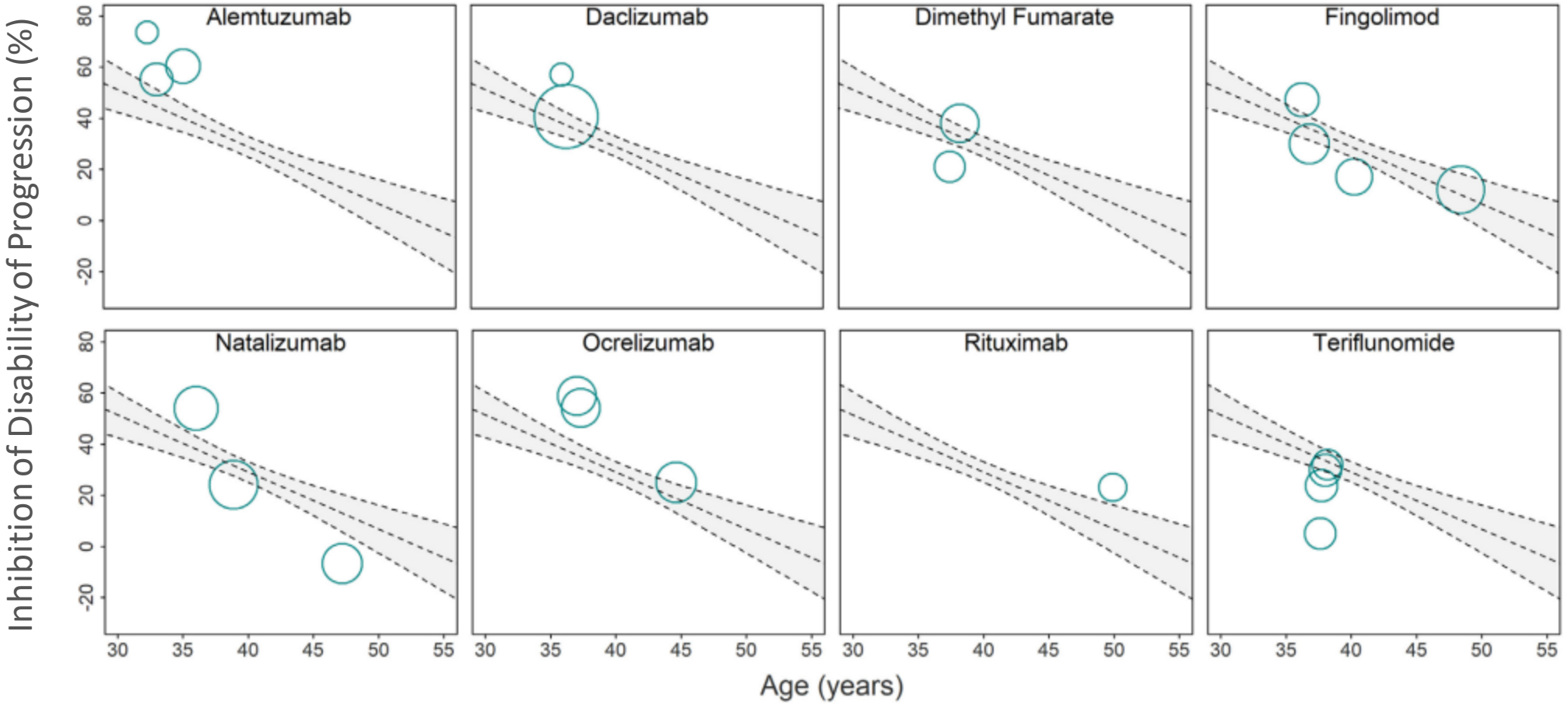
Question for the Panel: What role does age play in the selection of DMTs?

- Do you adjust DMT dose/interval in older individuals?
- In what circumstances would you consider stopping DMTs?

	ACUTE INFLAMMATION		SMOLDERING INFLAMMATION	
	ARR	T2/FLAIR/Gd	CDA/PIRA	Brain Volume
Fumarates	↓ <40 y		↓ <40 y	
Fingolimod	↓ <40 y		⊘	
Siponimod			↓ <50 and >50 y	
Ozanimod	↓ <40 y			
Cladribine	↓ <40 and >40 y		↓ <40 and >40 y	
Teriflunomide	↓ <38 and >38 y		↓ <38 yo	
Ocrelizumab	↓ <45 and >45 y	↓ NEDA <40 and >40 y	↓ <45 and >45 y	
Ofatumumab	↓ <40 and >40 y		↓ <40 and >40 y	
Natalizumab	↓ <40 and >40 y		↓ <40 y	

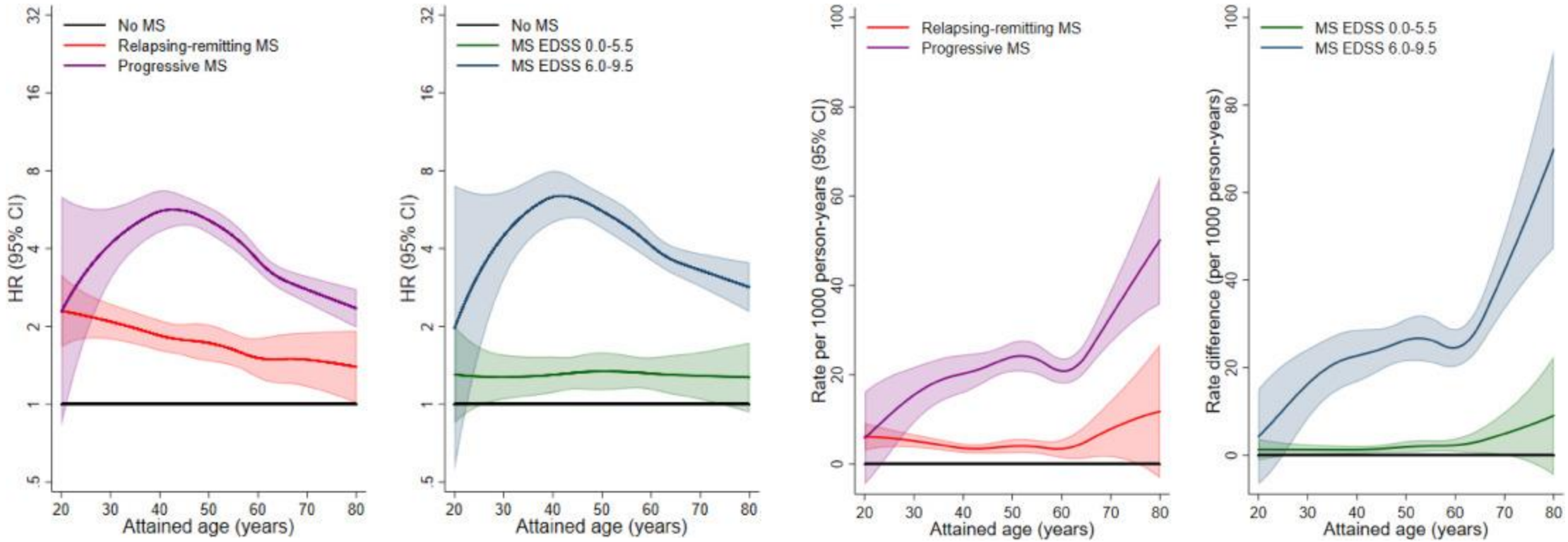
Weideman AM, et al. *Front Neurol*. 2017;8:577.

Efficacy of MS Drugs Is Linked to Age

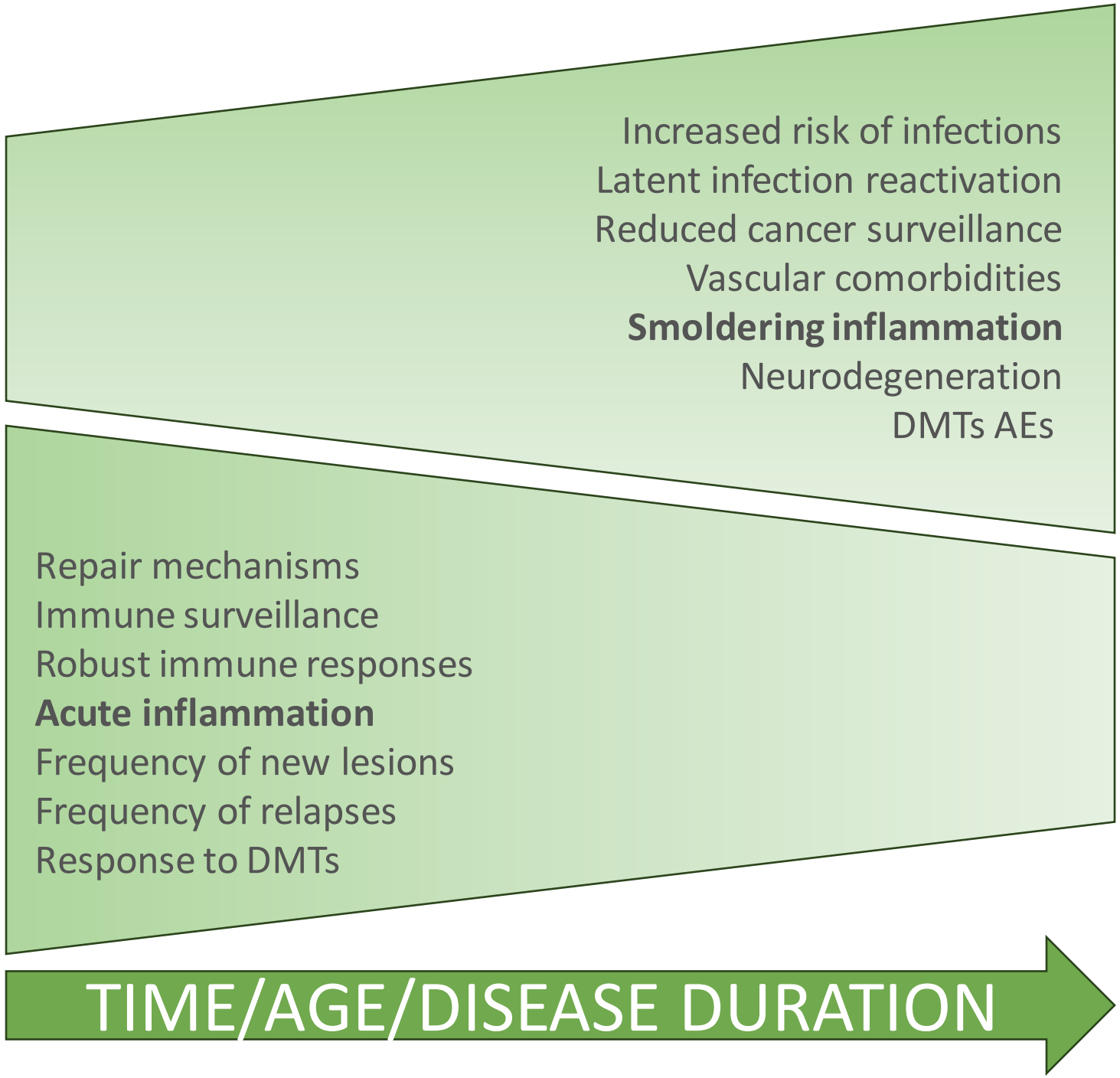


Weideman AM, et al. *Front Neurol*. 2017;8:577.

Risks of Serious Infection Associated with MS Disease Course and Disability by Attained Age



Brand JS, et al. *Brain Behav Immun Health*. 2022;22:100470.


Increased risk of infections
Latent infection reactivation
Reduced cancer surveillance
Vascular comorbidities
Smoldering inflammation
Neurodegeneration
DMTs AEs
Repair mechanisms
Immune surveillance
Robust immune responses
Acute inflammation
Frequency of new lesions
Frequency of relapses
Response to DMTs
TIME/AGE/DISEASE DURATION

Case 2: Continued

- UA confirmed the presence of infection. He was started on antibiotic therapy
- US revealed residual urine via post voiding ≥150 ml
- After discussing options, Mike elected to start oral cladribine

In Summary

- Age results in increased risks of infections, and complications from DMTs
- Over time, inflammation in MS becomes compartmentalized in the CNS
- Efficacy and safety of current DMTs is influenced by age
- Careful monitoring and surveillance for infections is necessary in older individuals with MS

Case #3: Exploring Measures of Disease Progression

Tirisham Gyang, MD

Assistant Professor of Neurology

Division Director, Multiple Sclerosis and Neuroimmunology

Wexner Medical Center

The Ohio State University

Columbus, OH

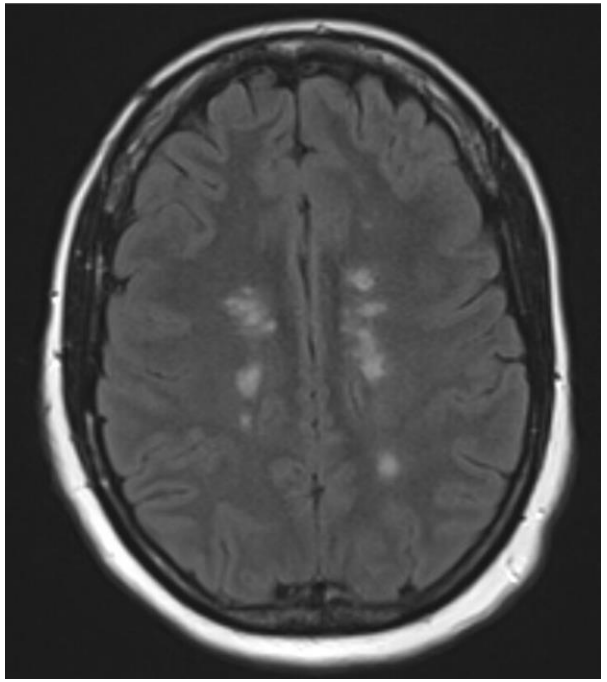
gna Global Neurology Academy

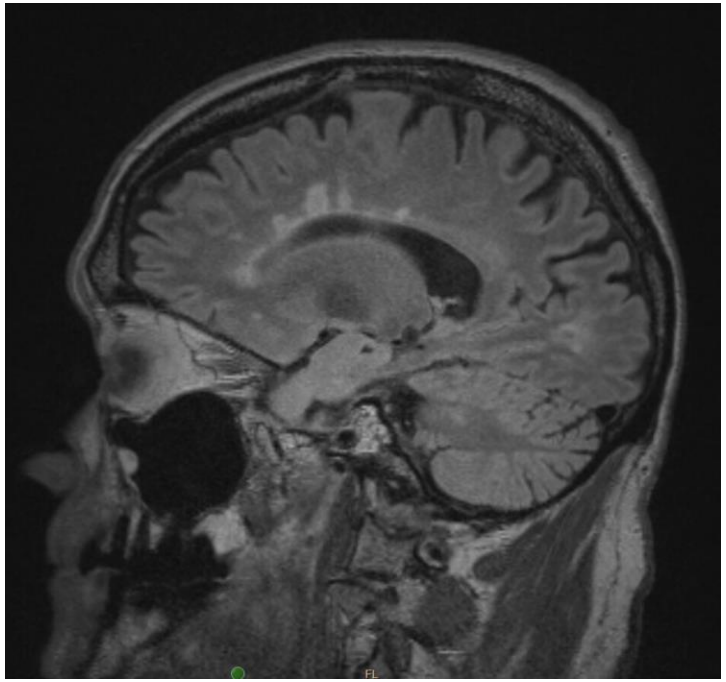
Case 3: K.R.

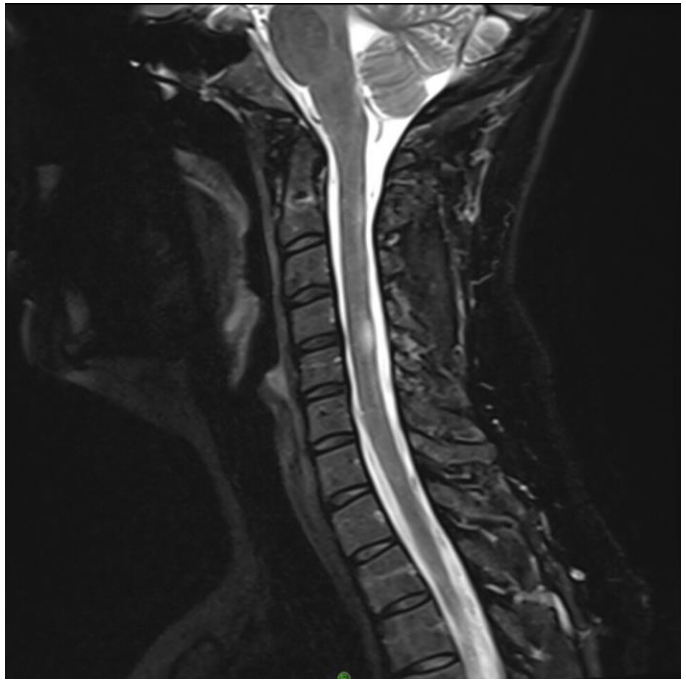
30-year-old woman with relapsing-remitting MS (RRMS) transferring care to a new provider

- 2010, developed chronic fatigue, brain-fog and mood dysfunction. She was diagnosed with depression and started sertraline.
- 2011, acute transient (1-week) vertigo while on vacation
- 2013, presented to the ED with acute right arm and leg paresthesia. MRI revealed multi-focal T2 lesions in the brain and cervical spine consistent with MS with an active lesion at C4-C5. CSF analysis revealed 6 unmatched bands in CSF.
  - She was diagnosed with RRMS and started interferon glatiramer acetate

Case 3: K.R.







Case 3: K.R.

She has had no further relapses over the last decade while on glatiramer acetate

However, within the last 5 years, she reports:

- Increasing difficulty keeping up with her job as a grocery store cashier
- Frequent falls (at least once a month) while walking her dog/playing with her kids
- Poorly controlled anxiety and fatigue

- Neurological exam:
  - Generally brisk deep tendon reflexes, mild proximal right LE weakness, slightly wide based gait with moderate ataxia.
  - **Timed 25ft walk: increased steadily by 35% between 2013 to 2023**
- Serial MRI scans: 2013-2023
  - No new T2 lesion, and no new T1 contrast-enhancing lesion
  - Visible mild generalized volume loss on brain MRI

Case 3: K.R.

- She tolerates glatiramer acetate well and wishes to remain on it given the “stability” in her MRI scans and the lack of clinical relapses
- She is very apprehensive about high-efficacy disease modifying therapies (DMTs) due to her concerns about the risks of chronic immunosuppression
- She acknowledges that her overall functional status has slowly declined over the last several years

Questions for the Panel:

- How would you approach the discussion about her disease stability or lack thereof?
- Would she benefit from switching to a more potent disease modifying therapy?

Measurement of Treatment Response

- Commonly used clinical measures
  - Clinical relapse
  - Neurological exam
  - MRI – T2 burden, T1 active lesions, and T1 black holes
  - EDSS

- Additional tools that may provide a better estimate of slow progression
  - Timed 25ft walk (T25FW) — Increase of ≥20% clinically significant
  - 9 Hole Peg test
  - Neuropsychological assessment
  - Symbol digit modalities test (SDMT)
  - Optical Coherence Tomography (OCT)
  - Advanced neuroimaging techniques
    - Brain/cord atrophy, paramagnetic rim lesions
  - Patient reported outcomes (PROs)
  - Novel biomarkers, eg, NfLs, GFAP

PIRA: How Much Does it Matter?

JAMA Neurology | Original Investigation

Association of Early Progression Independent of Relapse Activity With Long-term Disability After a First Demyelinating Event in Multiple Sclerosis

Carmen Tur, MD, PhD; Pere Carbonell-Mirabent, MSc; Álvaro Cobo-Calvo, MD, PhD; Susana Otero-Romero, MD, PhD; Georgina Arrambide, MD, PhD; Luciana Midaglia, MD; Joaquín Castilló, MD, PhD; Ángela Vidal-Jordana, MD, PhD; Breogán Rodríguez-Acevedo, MD; Ana Zabalza, MD; Ingrid Galán, MD; Carlos Nos, MD; Annalaura Salerno, MD; Cristina Auger, MD; Deborah Pareto, PhD; Manuel Comabella, MD, PhD; Jordi Río, MD, PhD; Jaume Sastre-Garriga, MD, PhD; Àlex Rovira, MD; Mar Tintoré, MD, PhD; Xavier Montalban, MD, PhD

- One-fourth of all patients presenting with a first demyelinating event may develop a first PIRA event within the first 12 years after symptom onset
  - 10% may do so within the first 5 years
- PIRA was associated with a sustained accumulation of disability and unfavorable long-term outcomes
- Early PIRA was associated with an even worse prognosis, independent of the inflammatory burden at the time of the first demyelinating attack

Tur C, et al. *JAMA Neurol*. 2023;80(2):151-160.

DMTs and PIRA

Progression is independent of relapse activity in early multiple sclerosis: a real-life cohort study

Emilio Portaccio,[1,2] Angelo Bellinvia,[1] Mattia Fonderico,[1] Luisa Pastò,[1] Lorenzo Razzolini,[1] Rocco Totaro,[3] Daniele Spitaleri,[4] Alessandra Lugaresi,[5,6] Eleonora Cocco,[7] Marco Onofrj,[8] Franco Di Palma,[9] Francesco Patti,[10] Davide Maimone,[11] Paola Valentino,[12] Paolo Confalonieri,[13] Alessandra Protti,[14] Patrizia Sola,[15] Giacomo Lus,[16] Giorgia Teresa Maniscalco,[17] Vincenzo Brescia Morra,[18] Giuseppe Salemi,[19] Franco Granella,[20] Ilaria Pesci,[21] Roberto Bergamaschi,[22] Umberto Aguglia,[23] Marika Vianello,[24] Marta Simone,[25] Vito Lepore,[26] Pietro Iaffaldano,[27] Massimo Filippi,[28,29] Maria Trojano[27] and Maria Pia Amato[1,2] on behalf of the Italian Multiple Sclerosis Register Centers Group

- Longer exposure to DMTs associated with a lower risk of both PIRA and relapse-associated worsening

- High efficacy DMTs may be more effective in preventing worsening of PIRA
  - Pooled analysis of 2 randomized clinical trials
  - Ocrelizumab was superior to interferon β-1a in preventing PIRA

Portaccio E, et al. *Brain*. 2022;145(8):2796-2805.

Early Intervention is Critical

- Early use of high efficacy DMTs is critical in the prevention of long-term disability in RRMS patients exhibiting early PIRA
- DMT escalation should be considered despite the absence of clinical relapse and/or lack of new T2 lesions or active T1 lesions
- Appropriate discussion on risk vs. benefit of highly effective therapies should factor in the increased risk of adverse long-term disability in patients exhibiting PIRA who are not treated adequately

Advanced MRI Techniques

JAMA Neurology | Original Investigation

Association of Brain Atrophy With Disease Progression Independent of Relapse Activity in Patients With Relapsing Multiple Sclerosis

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- RRMS patients with PIRA exhibit increased rates of tissue loss in several brain areas compared with patients who are clinically stable

Association of Spinal Cord Atrophy and Brain Paramagnetic Rim Lesions With Progression Independent of Relapse Activity in People With MS

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- RRMS and PMS patients with PIRA exhibited higher loads of PRLs (paramagnetic rim lesions)
- Patients experiencing PIRA had increased cervical cord atrophy both cross-sectionally at baseline and longitudinally during follow-up

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Cagol A, et al. *Neurology*. 2024;102(1):e207768.

Case 3: K.R.

- Further discussion with the patient on PIRA, risks vs. benefits of highly effective DMTs and additional testing to monitor insidious progression in disease course
- After obtaining pre-treatment labs, we agreed to switch to natalizumab (JCV seronegative)
  - K.R. preferred this option to avoid systemic immune suppression
- Additional assessments: neuropsychological assessment, OCT, PROs
- Referrals to physical therapy, psychiatry, and MS QoL clinic to optimize symptomatic management

Take-Home Points

- Insidious progression in the absence of relapses begins very early in a significant proportion of RRMS patients
- Early PIRA is associated with unfavorable long-term outcomes
- Innovative measures should be incorporated into clinical practice to monitor and identify RRMS patients who develop PIRA
- High efficacy DMTs should be considered early in patients who exhibit PIRA regardless of relapse/MRI activity

Key Takeaways and Audience Q&A

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