

Live Virtual Symposium: Right Patient, Right Treatment, Right Time: Utilizing Early, High-Efficacy Therapies to Improve Outcomes in RRMS

Premiere Date: Thursday, June 4, 2020

6:30 PM - 8:00 PM ET (live)

Credit Expiration Date: Friday, June 4, 2021

Log-In: www.cmeoutfitters.com/RRMS2020

#MScare

LIVE FACULTY:

Joseph R. Berger, MD, FACP, FAAN, FANA

Anne H. Cross, MD

CHAIR:

Fred D. Lublin, MD, FAAN, FANA

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INFORMATION FOR PARTICIPANTS

Statement of Need

Recent studies have demonstrated the benefits of early and aggressive treatment strategies in reducing disability progression and the frequency of relapses in patients with relapsing remitting multiple sclerosis (RRMS), marking a paradigm shift in the treatment of patients with RRMS. The traditional escalation approach is now often set aside in favor of the more individualized “induction” approach, which utilizes “early and aggressive” treatment with high-efficacy disease-modifying therapies (DMTs) to treat patients with high-risk disease.

The induction approach requires selection of DMTs based on disease activity, prognostic factors, and patient characteristics. This is challenging for clinicians due to the expanding treatment landscape for RRMS and the lack of specific guidelines. Additionally, neurologists often lack the knowledge and competence to identify patients who are candidates for this approach.

In this CME Outfitters live virtual symposium, expert faculty will focus on the prognostic factors that should be considered when developing treatment plans for patients with MS, as well as the latest clinical data on approved and emerging DMTs, so that clinicians can confidently develop tailored treatment approaches based on individual patient characteristics and appropriately monitor treatment response, safety, and tolerability.

Learning Objectives

At the end of this CME/CE activity, participants should be able to:

- Select patients with RRMS who are likely to benefit from early treatment with high-efficacy DMTs.
- Develop tailored treatment approach based on individual patient characteristics.
- Apply the latest clinical data on approved and emerging DMTs in monitoring treatment response, safety, and tolerability.

The following learning objectives pertain only to those requesting CNE or CPE credit:

- Describe patients with RRMS who are likely to benefit from early treatment with high-efficacy DMTs.
- Summarize a tailored treatment approach based on individual patient characteristics.
- Explain the latest clinical data on approved and emerging DMTs in monitoring treatment response, safety, and tolerability.

Target Audience

Neurologists, MS specialists, PAs, nurse practitioners, nurses, and pharmacists

Financial Support

Supported by educational grants from Celgene Corporation, a Bristol Myers Squibb company and from Genentech, a member of the Roche Group.

CREDIT INFORMATION

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Type: knowledge-based

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Learning Formats: Live activity

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ABPN Diplomates may select any CME activity relevant to their practice to count towards ABPN MOC requirements.

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This activity counts towards MIPS Improvement Activity requirements under the Medicare Access and CHIP Reauthorization Act of 2015 (MACRA). Clinicians should submit their improvement activities by attestation via the CMS Quality Payment Program website.

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Post-tests, credit request forms, and activity evaluations must be completed online (requires free account activation), and participants can print their certificate or statement of credit immediately (75% pass rate required). This website supports all browsers except Internet Explorer for Mac. For complete technical requirements and privacy policy, visit <https://www.cmeoutfitters.com/privacy-and-confidentiality-policy>.

There is no fee for participation in this activity. The estimated time for completion is 90 minutes. Questions? Please call **877.CME.PROS**.

FACULTY BIOS & DISCLOSURES

Fred D. Lublin, MD, FAAN, FANA (Chair)

Dr. Lublin is the Saunders Family Professor of Neurology at The Icahn School of Medicine at Mount Sinai and Director of the Corinne Goldsmith Dickinson Center for Multiple Sclerosis at that institution.

Dr. Lublin received his medical degree in 1972 from Jefferson Medical College, Philadelphia, PA. He completed his internship in Internal Medicine from the Bronx Municipal Hospital, Albert Einstein Medical Center, and his residency at the New York Hospital, Cornell Medical Center.

As a neuroimmunologist, Dr. Lublin has a special interest in immune functions and abnormalities affecting the nervous system. He has been involved in both basic science and clinical research. He and his colleagues were among the first in the country involved with studies of Interferon beta-1b, which was approved by the Food & Drug Administration in 1993 to treat the relapsing-remitting form of multiple sclerosis (MS). He is currently involved with several new clinical research protocols on promising agents for treating various aspects of MS. He was chairman of the National MS Society (USA) advisory committee on clinical trials of new drugs in MS and the National Multiple Sclerosis Society's Research Programs Advisory Committee. He was a member of the National MS Society National Board of Directors. He is past Chair of the New York City/Southern New York Chapter of NMSS Clinical Advisory Committee. He is a member of the International Medical & Scientific Board of the Multiple Sclerosis International Federation. Dr. Lublin and his colleagues at the National MS Society have re-defined the clinical course definitions of MS, updated in 2014. He has chaired a task force on the ethics of placebo-controlled trials in MS. Dr. Lublin is a member of the international panel that periodically redefines the diagnostic criteria for MS (McDonald Criteria). Dr. Lublin is co-chair of the National Institute of Neurological Diseases and Stroke MS Common Data Element committee and a member of their steering committee. He is a member of the WHO Advisory Group for the Revision of ICD-10 Diseases of the Nervous System working group on demyelinating diseases of the central nervous system. He was a Co-Chief and founding Editor of the journal *Multiple Sclerosis and Related Disorders*.

Dr. Lublin has published numerous scientific articles and is a member of many professional societies and advisory boards. Dr. Lublin has served as a consultant to the National Institutes of Health and to many pharmaceutical/biotech companies in all phases of new drug development and in preparation for presentation to the FDA and their advisory panels. He was the Principal Investigator of the NIH-sponsored multicenter Combination Therapy study in MS. In June of 2019, Dr. Lublin was awarded the June Halper Lifetime Achievement Award from the Consortium of Multiple Sclerosis Centers.

Joseph R. Berger, MD, FACP, FAAN, FANA

Dr. Berger is Professor of Neurology and Associate Chief of the Multiple Sclerosis Division of the Department of Neurology at the Perelman School of Medicine at the University of Pennsylvania in Philadelphia.

Dr. Berger is a summa cum laude graduate of the Pennsylvania State University – Jefferson Medical College 5 Year Accelerated Medical Program and a member of the national medical honor society, Alpha Omega Alpha. He completed his residency in internal medicine at Georgetown University Hospital and his neurology residency at the University of Miami School of Medicine and is board certified in both internal medicine and neurology. In 1981, he joined the faculty of the University of Miami School of Medicine serving in both the Departments of Neurology and Internal Medicine. At that institution, he held the Whigham-Berger Endowed Chair for the study of neurological complications of HIV/AIDS, the first endowed chair for the study of the neurological complications of HIV/AIDS. From 1995 through 2013, Dr. Berger was the Chairman of the Department of Neurology at the University of Kentucky where he was the Ruth L. Works Professor of Neurology and director of the UK Multiple Sclerosis Clinic. He is a Fellow of the American College of Physicians, American Academy of Neurology, and the American Neurological Association (ANA). In 2014 he was the recipient of the Pioneer Award from the International Society of Neurovirology and gave the prestigious Raymond D. Adams Lecture at the annual meeting of the ANA. In 2015 he was awarded the Distinguished Teaching Award from the ANA. In 2018, he received the Annual Alumni Achievement Award from the Sidney Kimmel Medical College, Thomas Jefferson University. His research interests include progressive multifocal leukoencephalopathy, the neurological complications of HIV/AIDS, multiple sclerosis, and other inflammatory disorders of the brain. He has published more than 250 refereed papers, more than 100 chapters, and has co-edited three textbooks (Berger JR and Levy RM: AIDS and the Nervous System, 2nd edition, Raven Press, New York, 1996; Nath A, Berger JR: Clinical Neurovirology, Marcel Dekker, New York, 2003 (2nd edition forthcoming in 2019); Portegies P, Berger JR: HIV/AIDS and the Nervous System, Elsevier, Amsterdam, 2007). Dr. Berger co-founded and chaired the first international conference on the neurological complications of HIV, the Neuroscience of HIV meeting. He also established the Commonwealth Neurological Society for neurologists in the state of Kentucky. Dr. Berger has a longstanding interest in international health and was one of the founding members of People-to-People, an organization for HIV/AIDS care and education in East Africa.

Anne H. Cross, MD

Dr. Cross is a professor of Neurology at Washington University in St. Louis, where she holds the Manny & Rosalyn Rosenthal and Dr. John L. Trotter MS Center Chair in Neuroimmunology and has served as Section Head of the Neuroimmunology/MS Section since 2001.

Raised in Mobile, Alabama, Dr. Cross graduated cum laude from the University of Alabama School of Medicine and was selected for the Alpha Omega Alpha medical honorary. After residency training in adult neurology at George Washington University, she spent several years as a post-doctoral fellow training in neuroimmunology and neuropathology at the National Institute of Health with Drs. Dale McFarlin and Henry McFarland and later at Albert Einstein College of Medicine with Drs. Cedric Raine and Celia Brosnan. Dr. Cross pursued further training in the clinical care of MS patients at Albert Einstein College of Medicine with Dr. Labe Scheinberg and received the Harry Weaver Neuroscience Scholar award of the National Multiple Sclerosis Society in 1990 and the John Jay Dystel Prize in 2019.

Dr. Cross joined the Washington University Department of Neurology in 1991. Her research has been continually funded by the National MS Society, the NIH and/or the U.S. Department of Defense since she opened her laboratory in 1991. Her laboratory currently focuses on advanced imaging studies of progressive MS and the role(s) of B cells and B cell products in MS and its animal models. During her nearly 30 years at Washington University, she has trained more than 30 students, residents, and fellows; she is very proud that they all continue to actively contribute to the research and care of MS and related diseases.

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Dr. Lublin reports that he receives research support from Actelion Pharmaceuticals; Biogen; Brainstorm Cell Therapeutics Inc; National Institutes of Health (NIH); National Multiple Sclerosis Society (NMSS); Novartis; and Sanofi. He has consulting agreements, serves on advisory boards, or Data and Safety Monitoring Board for Acorda Therapeutics; Actelion Pharmaceuticals/Janssen Pharmaceuticals, Inc.; Apitope; Brainstorm Cell Therapeutics Inc.; Avotres; Biogen; 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; and TG Therapeutics. He is a speaker for Sanofi (non-promotional).

Dr. Berger reports he received research support from Biogen and Genentech, Inc. He serves on the advisory committee for Excision BioTherapeutics; Inhibikase Therapeutics, Inc.; and Novartis. He serves as a consultant for Amgen Inc.; Biogen; Celgene Corporation; Dr. Reddy's Laboratories; Encycle Therapeutics; Genentech, Inc./Roche; Mapi-Pharma; Merck & Co., Inc.; Morphic Therapeutic; Novartis; EMD Serono, Inc.; and Shire.

Dr. Cross reports she receives research support from The Conrad N. Hilton Foundation and U.S. Department of Defense. She serves on the advisory committee for EMD Serono, Inc. and Genentech, Inc./Roche. She is consultant for Biogen; Celgene Corporation; EMD Serono, Inc.; Genentech, Inc./Roche; and Novartis.

Jeffrey Helfand, DO (peer reviewer) has no disclosures to report.

Mae Ochoa, RPh (peer reviewer) has no disclosures to report.

Alaeddin Abukabda, MS, DMD, PhD (planning committee) has no disclosures to report.

Evan Luburger (planning committee) has no disclosures to report.

Jan Perez (planning committee) has no disclosures to report.

Sharon Tordoff (planning committee) has no disclosures to report.

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**RIGHT PATIENT,
RIGHT TREATMENT,
RIGHT TIME:**
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Therapies to Improve
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This symposium is
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3. Be sure to fill in your **ABIM ID number** and **DOB (MM/DD)** on the evaluation, so we can submit your credit to ABIM.



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- Complete the follow-up survey from CME Outfitters in approximately 3 months

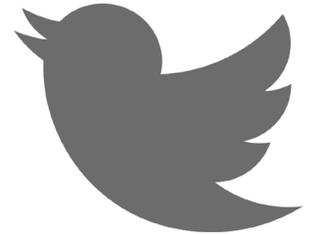
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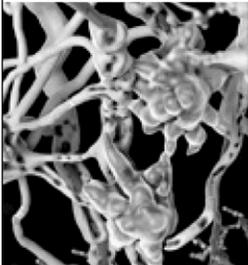
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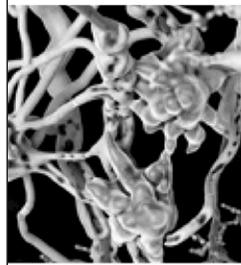
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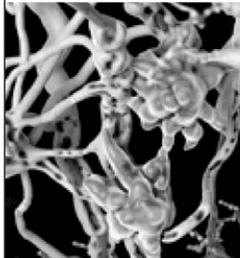
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Learning Objective 1

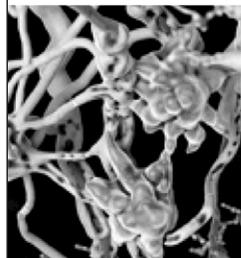
Select patients with RRMS who are likely to benefit from early treatment with high efficacy DMTs.





Learning Objective 2

Develop tailored treatment approaches based on individual patient characteristics.



Learning Objective 3

Apply the latest clinical data on approved and emerging DMTs in monitoring treatment response, safety, and tolerability.



Clinical Case: Julie

- 22-year-old white female with no significant prior medical history
- Sudden onset of blurred vision in right eye and pain on eye movement
- Fatigue and enervation with heat over 1 year
- Denies Lhermitte's sign, vertigo, diplopia, sphincter dysfunction, paresthesia or numbness, weakness, and imbalance



CME Outlines

Multiple Sclerosis Classifications

- Clinically isolated syndrome (CIS)
- Radiologically isolated syndrome (RIS)
- 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

Sand KI. *Curr Opin Neurol.* 2015;28(3):193-205.

CME Outlines

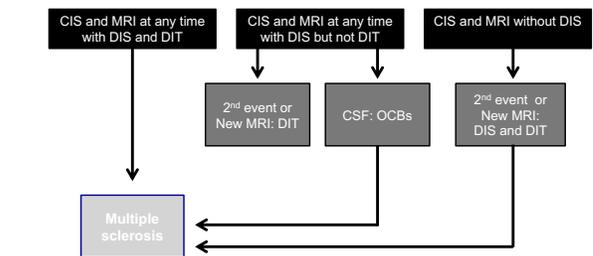
Current Diagnostic Criteria for RRMS

- Patients with ≥ 2 clinical MS attacks with clinical evidence of ≥ 2 lesions or evidence of 1 lesion with evidence of a prior attack involving a lesion in distinct anatomic location
 - No further evidence needed
- Patients with history of ≥ 2 attacks with clinical evidence of only 1 lesion
 - Additional evidence on MRI for hyperintense lesions or development of an additional clinical attack

Thompson AJ, et al. *Lancet Neurol.* 2017;17(2):162-173.

CME Outlines

Current Diagnostic Criteria for RRMS

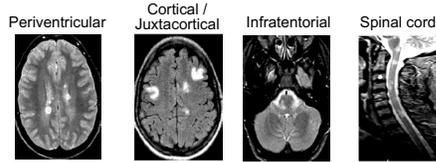


CIS = clinically isolated syndrome; CSF = cerebrospinal fluid; DIS = dissemination in space; DIT = dissemination in time; MRI = magnetic resonance imaging; OCB = oligoclonal band
Thompson AJ, et al. *Lancet Neurol.* 2017;17(2):162-173.

CME Outlines

Diagnostic Criteria MRI

DIS: ≥ 1 T2 lesions in ≥ 2 locations



- 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.* 2017;17(2):162-173.



Clinical Case: Julie

- Exam shows VA 20/20 in OS, but 20/30 OD with color desaturation on right eye
- CSF shows normal cell count, normal protein, and 8 OCBs
- Alternative diagnoses for optic neuritis were ruled out

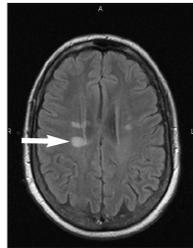


OCB = oligoclonal band; OD = oculus dexter (right eye); OS = oculus sinister (left eye)



Clinical Case: Julie – MRI Findings

- Several hyperintense lesions
 - None contrast enhancing
 - None in infratentorial compartment
- Enhancement of right optic nerve
- No parenchymal lesions



Predictors of Poor Prognosis in MS

Demographic and environmental factors

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

MRI observations

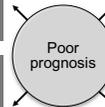
- A high number of T2 lesions
- A high T2 lesion volume
- The presence of gadolinium-enhancing lesions
- The presence of infratentorial lesions
- The presence of spinal cord lesions
- Whole brain atrophy
- Grey matter atrophy

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

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 fiber layer thinning detected with optical coherence tomography



IgG = immunoglobulin G; IgM = immunoglobulin M.
 Rolstein D, X Montalban. *Nat Rev Neurol.* 2019;15(5):287-300.



Disease Modifying Medications: Categories

Immunomodulators

Interferon-b
Glatiramer Acetate
DMF
Teriflunomide

- Pros**
- Safety
 - Long term experience
- Cons**
- Modest efficacy
 - Many injectable

Cell-Trafficking Inhibition Agents

Natalizumab
Fingolimod
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
(Rituximab*)
(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 approved by the FDA for treatment of MS
Rozvi SA, et al. *Clinical Neuroimmunology*. 2nd ed. 2020.



Efficacy and Safety of Current Therapies

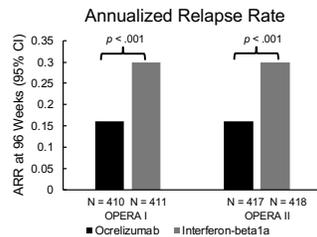
Agent	Cladribine ¹	Fingolimod ²	Alemtuzumab ³	Natalizumab ⁴
Relapse Rate Decrease	58%	54%	55%	68%
Comparator or Placebo	Placebo	Placebo	Interferon beta 1a	Placebo
Disability Progression Decrease	33%	30%	30%	42%
T2 Lesions Reduction	73.4%	74.5%	10%	82.7%
Safety	Contraindicated in HIV or active chronic infections Do not breastfeed within 10 days	Bradycardia, cardiac conduction disturbance, opportunistic infections, macular edema, decrease in pulmonary function, hepatic effects, teratogenicity	Secondary autoimmune conditions, infusion reactions, increased risk of malignancies	Herpes infections, blindness, hypersensitivity reactions, opportunistic infections

1. Giovannoni G, et al. *N Engl J Med*. 2010;362(5):416-426. 2. Calabresi PA, et al. *Lancet Neurol*. 2014;13(6):545-556. 3. Coles AJ, et al. *Lancet*. 2012;380(9856):1829-1839. 4. Polman CH, et al. *N Engl J Med*. 2006;354(9):899-910.



Ocrelizumab: Efficacy and Safety

- Opera I and II trials
 - N = 821, 835 respectively
- 94% and 95% reduction in Gd+ lesions in the ocrelizumab group vs interferon-beta 1a
- 46% and 47% reduction in ARR in ocrelizumab group vs. interferon-beta 1a
- Ocrelizumab did not increase risk of serious infections vs interferon-beta 1a in 5 years of safety data

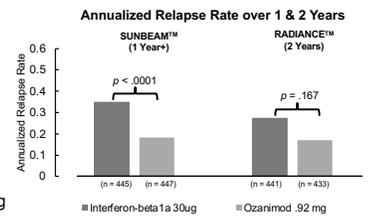


ARR = annualized relapse rate. The FDA recommends ocrelizumab patients follow standard breast screening guidelines.
Hauser SL, et al. *N Engl J Med*. 2017; 376:221-234.



Ozanimod: Efficacy and Safety

- SUNBEAM and RADIANCE trials
 - N = 1346, N = 1313 respectively^{1,2}
- 63% and 53% reduction in Gd+ lesions in ozanimod group versus interferon-beta 1a^{1,2}
- 48% and 38% reduction in ARR in patients receiving ozanimod vs interferon-beta 1a^{1,2}
- No clinically significant cardiac adverse effects, lymphopenia and macular edema in patients receiving ozanimod^{1,2}



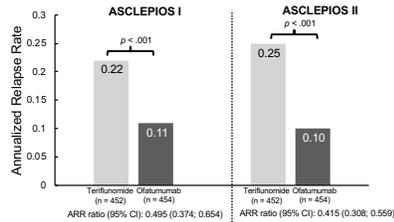
FDA approved maintenance dose of ozanimod for relapsing forms of MS = .92mg

1. Cohen JA, et al. *Lancet Neurol*. 2019;18(11):1021-1033. 2. Comi G et al. *Lancet Neurol*. 2019;18(11):1009-1020.



Ofatumumab*: Efficacy and Safety Emerging Therapy

- ASCLEPIOS I and II
 - N = 927, N = 954 respectively
- 97% and 93% reduction in Gd+ lesions in ofatumumab group vs teriflunomide
- 50.5% and 58.5% reduction in ARR in ofatumumab group compared to teriflunomide
- Demonstrated safety and tolerability profile with infection rates similar to teriflunomide



* This agent is not currently approved by the FDA for treatment in MS. Regulatory review expected in September 2020. Hauser SL et al. ECTRIMS 2019. Presentation 336.



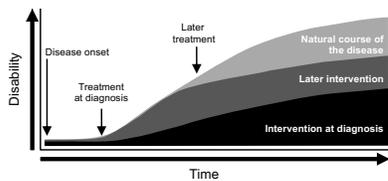
Making Treatment Decisions Considering the Benefits and Risks



Ross AP. Am J Manag Care. 2013;19(16):S301-S306



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(3 Suppl B):S4-11.



Timing of High Efficacy DMTs

- Early initiation of DMTs leads to improved disease control and long-term outcomes compared to delayed commencement
- Active MS management reduces relapse activity, disability accrual and irreversible brain atrophy

DMT = disease-modifying therapy. Merkel B, et al. Autimmun Rev. 2017;16(6):658-665.



Treatment Initiation Choices

High Efficacy (Higher Risk)

- Start with a higher efficacy agent
 - Obtain a treatment "response" for a given period of time
- Monitor for safety

vs.

Escalation (Lower Risk)

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

Lazibat I, et al. *Clin Antropol*. 2014;38(1):385-393.



Clinical Case - Jason

- 46-year-old African-American male
- Physician and is concerned because of his potential exposure to SARS-CoV2
- Tremor and incoordination that was first noticed 3 weeks earlier
- Paresthesia of both legs last 3 days 1 year earlier
- Slight visual blurring left eye, urinary frequency and urgency



Clinical Case - Jason

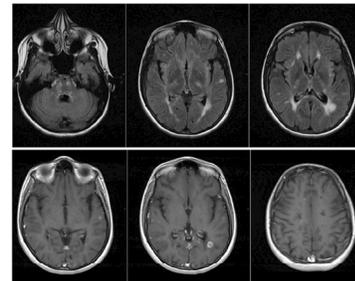
- Was diagnosed with MS in 2018
- Started on Interferon-B
- Slow cognition, pale left optic disk with RAPD, bilateral gaze evoked horizontal nystagmus
- Tremor of right upper extremity with dysmetria on F-N and H-S, diffusely brisk reflexes, abnormal tandem gait



F-N = finger to nose; H-S = heel to shin; RAPD = relative afferent pupillary defect



Clinical Case – Jason’s MRI Findings



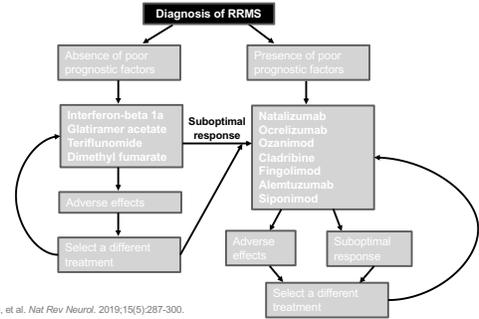
MS and COVID-19

- No current evidence suggests increased morbidity or mortality in MS patients with COVID-19¹
- Neurologists should counsel patients about how the relative risk of hospitalization and death due to COVID-19 may be affected by their neurologic condition and its management²
- Most deaths have occurred in older patients with multiple comorbidities and advanced disease who are often not on DMTs¹

1. Berger JP, et al. *Neurol Neuroimmunol Neuroinflamm*. 2020; 7(4):e761. 2. Rubin MA et al. *Neurol*. 2020;00:1-6.



Switching Therapy in RRMS



Adapted from Rotstein D, et al. *Nat Rev Neurol*. 2019;15(5):287-300.



SMART Goals

Specific, Measurable, Attainable, Relevant, Timely

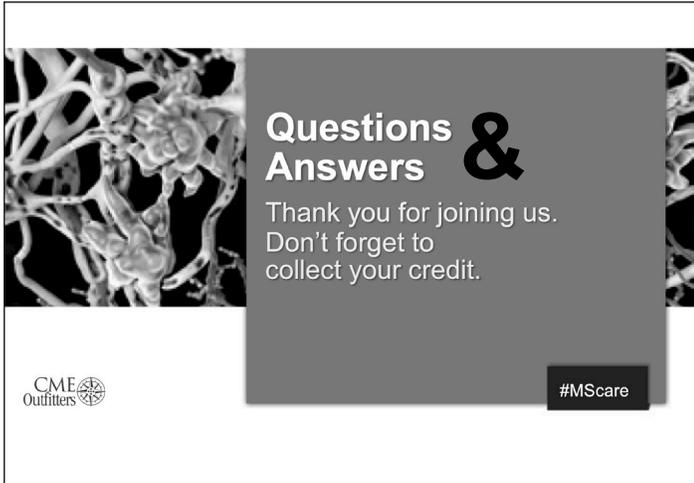
- Combine diagnostic features with prognosis to determine the therapeutic approach to RRMS
- Partner with patients to discuss treatment goals to optimize outcomes
- Integrate most recent clinical data into the treatment paradigm of patients with RRMS



Ask A Question

Click on the **Ask a Question** tab and type your question. Please include the faculty member's name if the question is specifically for them.



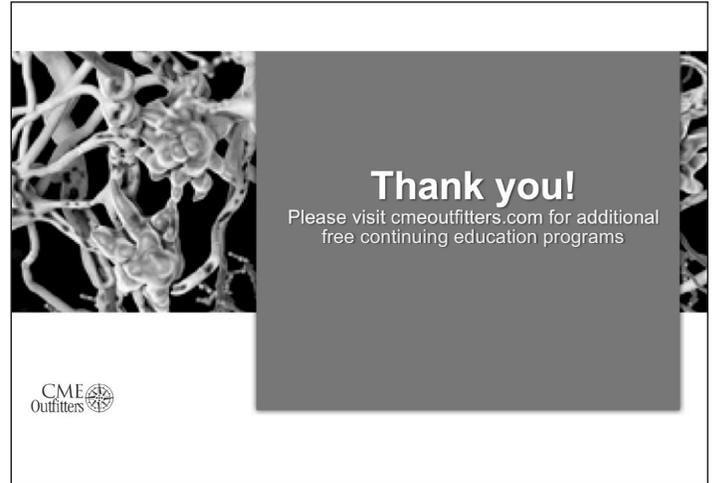


Questions & Answers

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Attendance Form for Groups

Please complete and FAX to **614.929.3600**

Activity Title and Faculty:

Live Virtual Symposium: Right Patient, Right Treatment, Right Time: Utilizing Early, High-Efficacy Therapies to Improve Outcomes in RRMS

with Fred D. Lublin, MD, FAAN, FANA (Chair), Joseph R. Berger, MD, FACP, FAAN, FANA, and Anne H. Cross, MD

Site/Institution Name: _____

Practice Setting: Office-based Hospital Clinic Managed Care Small Group Practice (less than 5)
 Large Group Practice (more than 5) Other: _____

Address: _____

City: _____ State: _____ ZIP: _____

Site Coordinator: _____ Phone: _____

Fax: _____ Email: _____

Completion Date: _____ We participated in: _____

Attendee Name (please print)	Please Circle Discipline							
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