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Education Initiative in Neurology
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A Sea Change in MS Treatment—
The Potential of Small Molecules

A CME/CE On Demand Webcast

www.clinicianschannel.com/cmscwebcast

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AGENDA

This CME/CE activity is supported by an educational grant from **Novartis Pharmaceuticals Corporation**

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CONTRACT FOR MUTUAL RESPONSIBILITY IN CME

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Sincerely,

Robert S. Stern
President
Projects In Knowledge, Inc.

Letter from the Chair

Dear Colleague:

Multiple sclerosis (MS) affects over 1,000,000 individuals world-wide, with many regions noting a significant increase in the incidence of this debilitating disease over the past 30 years. Fortunately, exciting new developments in understanding the pathophysiology and disease process of MS, coupled with emerging therapeutic agents now in clinical trials, offer the promise of new treatment strategies for physicians and new hope for patients with the disease. Recent advances in understanding the potential roles of vitamin D deficiency and Epstein Barr virus in the pathogenesis of MS may shed light on possible preventive measures that can be taken to mitigate the development of new cases, whereas recognition of the importance of early intervention in treating MS may help to prevent or delay future disability in patients already afflicted. In recent phase II clinical trials, novel small-molecule agents have effectively reduced GAD-enhancing lesions and relapse rates, indicating the possibility of expanded treatment options in the future.

In *A Sea Change in MS Treatment – The Potential of Small Molecules*, a panel of experts in the field will discuss these exciting new developments and the evolving strategies and controversies in optimizing outcomes for patients with MS.

We welcome you to this timely and informative webcast and hope that this discussion is useful to you in incorporating the new treatment options into your own practice.

Sincerely,

Bruce A. Cohen, MD

Professor

Davee Department of Neurology

Feinberg School of Medicine

Northwestern University

Chicago, Illinois

CHAIR

Bruce A. Cohen, MD

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Davee Department of Neurology
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Dr. Cohen received his medical degree from the University of Illinois College of Medicine at Chicago. Following a residency in internal medicine, he completed his residency in neurology at the McGaw Medical Center/Northwestern University Medical School (now the Feinberg School of Medicine, Northwestern University). Dr. Cohen is presently professor of neurology in the Davee Department of Neurology at the Feinberg School of Medicine, Northwestern University. He is an attending neurologist at Northwestern Memorial Hospital, a consulting neurologist at the Rehabilitation Institute of Chicago, and a member of the Northwestern Medical Faculty Foundation.

Dr. Cohen co-founded the Northwestern Comprehensive Multiple Sclerosis program at Northwestern University with Dr. James Sliwa from the Rehabilitation Institute of Chicago in 1986. This program combines medical and rehabilitative therapies with an integrated disease-specific approach. He is director of the multiple sclerosis clinical program in the Department of Neurology at Northwestern, where he and his colleagues treat multiple sclerosis patients and engage in clinical research on disease manifestations and treatment approaches.

Dr. Cohen has worked with the National MS Society for many years. He is a member and current chair of the Clinical Care Committee (2006–2009), and a member of the Medical Advisory Board of the National MS Society, New York. He is also a member and past chair of the Professional Advisory Committee of the National MS Society, Chicago and Greater Illinois Chapter.

Dr. Cohen has been active in clinical research on neurological complications of AIDS since 1986. He is an investigator in the Multicenter AIDS Cohort Study (MACS), the Neurological AIDS Research Consortium, where he directs the Northwestern University site, and the NIH AIDS Clinical Trials Group, where he is past chair of the neurology subcommittee (2004–2005), and a member of the neurology leadership committee.

Dr. Cohen is a Fellow of the American Academy of Neurology, the American College of Physicians, and the American Heart Association. He is an elected member of the American Neurological Association, a Diplomate of the American Board of Psychiatry and Neurology, and a Diplomate of the American Board of Internal Medicine.

Dr. Cohen's areas of interest include multiple sclerosis and related demyelinating disorders, and the neurologic complications of AIDS. He has published in numerous neurologic and medical journals, including the *New England Journal of Medicine*, *Neurology*, *Annals of Neurology*, and *Archives of Neurology*, and has contributed to numerous textbooks.

FACULTY

Bruce A.C. Cree, MD, PhD, MCR

Assistant Professor of Neurology
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Dr. Cree is an assistant professor of neurology at the University of California—San Francisco (UCSF) Multiple Sclerosis Center. He is board certified in neurology and also serves as an attending neurologist at the UCSF Medical Center.

After graduating from Brown University, in Providence, Rhode Island, Dr. Cree earned his medical degree and his PhD from UCSF. He completed his residency in neurology at New York Presbyterian Hospital (Columbia University), New York City, where he was chief resident. He later returned to UCSF, where he undertook postdoctoral subspecialty training in multiple sclerosis as a Sylvia Lawry fellow. Additionally, he received a master's degree in

clinical research at the UCSF department of epidemiology and biostatistics.

Dr. Cree has served as an investigator on numerous clinical studies in multiple sclerosis. Much of his research has focused on multiple sclerosis epidemiology, and his work has been published in *The American Journal of Human Genetics*, *Annals of Neurology*, *Archives of Neurology*, *Genes and Immunity*, *Journal of Allergy and Clinical Immunology*, *Nature Genetics*, *The Neurologist*, *Neurology*, and *Seminars in Neurology*.

FACULTY

Mark S. Freedman, HBSc, MSc, MD

Professor of Neurology
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Dr. Freedman is professor of neurology in the Department of Medicine at the University of Ottawa, Ontario, Canada; a Senior Scientist, Neuroscience, at the Ottawa Health Research Institute; and director of the Multiple Sclerosis Research Clinic at The Ottawa Hospital.

He earned his undergraduate and medical degrees at the University of Toronto, and also completed postgraduate training in clinical neurology, pediatric neurology, neuropathology, and neurophysiology. Dr. Freedman holds the specialist certifications FRCPC (Canada) and CSPQ (Quebec) in neurology and is a fellow of the American Academy of Neurology (FAAN).

Dr. Freedman's extensive research experience has focused primarily on basic neuroimmunology applied to clinical and therapeutic trials in multiple sclerosis. His research activities include investigation of the role of gamma delta T-cells in the pathogenesis of multiple sclerosis, the role of cytokines in multiple sclerosis disease progression or response to therapy, and antibody-dependent cell cytotoxicity via Fc receptors as a potential treatment for patients with multiple sclerosis. He is a prominent clinical researcher associated with peer-reviewed and industry-related funding, investigating immune mechanisms of multiple sclerosis and the exploration of potential multiple sclerosis therapies, including stem cell transplantation.

Dr. Freedman is the author or co-author of more than 100 articles, book chapters, and abstracts, and is an ad hoc reviewer for several international journals and granting agencies. An internationally renowned speaker, Dr. Freedman has given hundreds of lectures and keynote presentations on emerging therapies associated with multiple sclerosis. He is a member of the MS Society of Canada, the U.S. Multiple Sclerosis Society, and the Consortium of Multiple Sclerosis Clinics. Dr. Freedman serves as consultant, advisor, and member of several data safety monitoring boards for many research and pharmaceutical corporations.

FACULTY

Douglas S. Goodin, MD

Professor of Neurology
Medical Director
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San Francisco, California

Dr. Goodin is director of the Multiple Sclerosis Center at the University of California–San Francisco (UCSF) Medical Center. He is a neurologist and an internationally renowned expert in the treatment and research of multiple sclerosis. He earned his bachelor of science degree in genetics and biochemistry at the University of Washington in Seattle; his master of science degree in molecular biology at Purdue University in Indiana; and his medical degree from the University of California, Irvine. He completed a residency in neurology at UCSF, where he joined the medical center staff in 1982. Dr. Goodin also is a professor of neurology at UCSF. In addition to multiple sclerosis, Dr. Goodin's research interests include various forms of dementia.

PROGRAM INFORMATION

TARGET AUDIENCE

This CME activity is designed for neurologists and other clinicians who are involved in the treatment of patients with multiple sclerosis.

ACTIVITY GOAL

The goal of this program is to provide clinicians with state-of-the-science, clinically relevant information concerning the pathophysiology of MS, novel treatments in development, and new strategic approaches that will enable them to optimize therapy for their patients with MS.

LEARNING OBJECTIVES

- Assess the etiology, pathophysiology, and course of MS in order to determine appropriate treatment approaches that improve patient outcomes.
- Understand the inflammatory and neurodegenerative response in MS and potential targets for intervention to select optimal strategies for the care of MS patients.
- Understand the MOA, efficacy, and safety of current and emerging agents used in the treatment of patients with MS.

CME INFORMATION: PHYSICIANS

Statement of Accreditation

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This program is approved for 1.5 contact hours.

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Bruce A.C. Cree, MD, PhD, MCR, has received grant/research support from Bio MS Medical, EMD-Serono, and Genentech, Inc; and has participated in the speakers bureaus of Biogen-Idec and Teva Neuroscience.

Mark S. Freedman, HBSc, MSc, MD, has no potential conflicts of interest to disclose.

Douglas S. Goodin, MD, has received grant/research support from Bayer Pharmaceuticals, Biogen-Idec, Novartis Pharmaceuticals Corporation, and Schering-Plough Corporation; has served as a consultant for Bayer Pharmaceuticals, EMD-Serono, and Schering-Plough Corporation; has participated in the speakers bureaus of Bayer Pharmaceuticals, EMD-Serono, Schering-Plough Corporation, and Teva Neuroscience; has received consulting fees from Bayer Pharmaceuticals, EMD-Serono, and Schering-Plough Corporation; and has received honoraria directly from Bayer Pharmaceuticals, EMD-Serono, Schering-Plough Corporation, and Teva Neuroscience.

Peer Reviewer has no significant relationships to disclose.

Projects In Knowledge's staff members have no significant relationships to disclose.

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This independent CME/CE activity is supported by an educational grant from **Novartis Pharmaceuticals Corporation.**

New Perspectives on the Pathogenesis of MS

Douglas S. Goodin, MD

Five to 200 individuals out of every 100,000 people develop multiple sclerosis (MS), with women and those of Caucasian ancestry disproportionately at risk. Although it has been known for some time that there is evidence demonstrating a genetic predisposition for the disease, it is apparent that environmental factors are also involved. In addition, it appears that the timing of exposure to these environmental factors is critical, since individuals migrating prior to age 15 years from an area of high MS prevalence to an area of low prevalence (or the reverse) tend to adopt a prevalence similar to the region to which they have immigrated, whereas, those who immigrate at a later age maintain the risk of the area from which they originated. Epidemiologic evidence indicates that there are at least three environmental events that must occur in the pathogenesis of MS—one operating in utero or in the early postnatal period; the second beginning sometime after birth and continuing to operate until approximately 15 years of age; and the third operating in adulthood, long after the first and second events have taken place. The most likely candidates for the first two of these environmental factors are vitamin D deficiency and Epstein Barr virus (EBV) infection. Evidence for the involvement of vitamin D comes from a variety of sources. Vitamin D production in humans requires exposure to UVB in the skin, and the latitude gradient of UVB is strikingly similar to the prevalence of MS. Moreover, the rate of skin cancer in patients with MS is half that of controls, although the rates of other cancers are similar, suggesting reduced exposure to UVB. Other studies have shown a negative association between sun exposure during childhood and adolescence and the development of MS. In geographic areas of high MS prevalence, populations that consume high levels of vitamin D have a lower incidence of MS than others in the region, and additional studies have shown that women with the highest quintile for total vitamin D consumption have significantly lower rates of MS than those in the lowest quintile. Since vitamin D is known to be involved in immune development and its deficiency is associated with autoimmunity, it is likely to be the first environmental factor involved in the pathogenesis of MS. On the other hand, EBV infection is a more probable candidate for the second factor, as it does not usually occur in utero or in the early postpartum period. Although evidence of EBV infection is ubiquitous among both people with MS and unaffected individuals, there is a statistical association between EBV infection and MS. Furthermore, both late EBV infection and mononucleosis are associated with MS. A mathematical model incorporating genetic susceptibility and environmental factors has been developed for the pathogenesis of the disease. Finally, the incidence of MS is increasing in many regions. Since this phenomenon has been noted only during the last 30 years, a period that is too short to result in genetic changes, the increase is probably related to changes in environmental exposure.

Suggested Readings

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Goals of Optimal Therapy

Bruce A. Cohen, MD

The goals of therapy in treating patients with multiple sclerosis (MS) are to prevent disability and relapses, relieve symptoms, maintain well-being, and optimize quality of life. Current disease-modifying therapies are much more successful in achieving some of these goals than others, suppressing relapses and enhancing MRI lesions more effectively than preventing progressive disability later in the course of disease. In a recent meta-analysis of placebo patients from MS treatment trials, more than 40% of patients who relapsed had an increase in EDSS score 3 or more months after the relapse. In the natural history of MS, although relapses decrease over time, disability worsens. Results from a number of investigations suggest that treatment early in the course of disease may help to reduce this risk of future disability. In a trial of interferon beta in patients with relapsing-remitting MS, treatment not only reduced relapses and MRI activity but also was more effective in reducing EDSS progression when given for 4 years than when administered for 2 years following 2 years of placebo. Another study demonstrated that interferon beta therapy at CIS presentation reduced the risk of EDSS worsening over 3 years. MRI studies have also shown that T2 burden at CIS presentation predicts later disability, suggesting that treatment early in the course of disease may prevent these lesions from accumulating and preventing future disability. A recent hypothesis provides a theoretic basis for the need to treat patients early in their disease. In this model, early damage in MS is compensated for by the expansion of neural networks that permits the individual to maintain performance for a time. However, when this "cerebral reserve" is exceeded, persistent detectable deficits in function occur. The implication of this hypothesis is that immune therapy early in the course of disease, while the patient still has a reserve of compensating neurons, may alter the course of disease, preventing progressively worsening disability in the future. Nevertheless, despite the advantages of early therapy, suboptimal response—due to nonadherence, genetic variations in response to interferon beta, neutralizing antibodies, and other factors—will continue to impact the ability to achieve therapeutic goals, pointing to the need for careful monitoring at all stages of treatment.

Suggested Readings

Brex PA, Ciccarelli O, O'Riordan JI, et al. A longitudinal study of abnormalities on MRI and disability from multiple sclerosis. *N Engl J Med*. 2002;346:158-164.

Kappos L, Freedman MS, Polman CH, et al. Effect of early versus delayed interferon beta 1-b treatment on disability after a first clinical event suggestive of multiple sclerosis: a 3-year follow-up analysis of the BENEFIT study. *Lancet*. 2007;370:389-397.

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Current Therapies and Role of Emerging Small-Molecule Therapies in MS—Evolving Strategies

Bruce A. C. Cree, MD, PhD, MCR

Multiple sclerosis (MS) is believed to be a heterogeneous disease caused by multiple mechanisms. Since no single therapy is effective against all these mechanisms, new agents with novel mechanisms of action are needed. Five promising small-molecule oral agents are now in phase III development—fingolimod, fumarate, teriflunomide, laquinimod, and cladribine. Fingolimod, a sphingosine-1-phosphate receptor modulator, induces rapid and reversible sequestration of lymphocytes in lymph nodes, preventing activated and autoreactive cells from migrating to target organs. Fingolimod also crosses the blood brain barrier and may have neuroprotective properties. In phase II trials, fingolimod significantly reduced cumulative Gad+ lesions by 43% and annualized relapse rate by 55%. These benefits were sustained at 36 months, with 68% to 73% of patients (depending on dosage) remaining relapse-free and 89% free of Gad+ MRI lesions. Fumarate is derived from the common fumitory plant and has long been used to treat skin disorders. It inhibits T-cell activity by inducing activated lymphocyte apoptosis and shifting T-cell balance from Th1 to Th2. It may also have neuroprotective properties through its activation of antioxidant response genes. Compared with placebo, fumarate resulted in a significant 69% reduction in the number of new Gad+ lesions from weeks 12 to 24 in a phase II trial. Teriflunomide inhibits pyrimidine synthesis and T cell division, as well as murine experimental autoimmune encephalomyelitis (EAE). However, it is teratogenic in animals and its use is not advised in patients of either gender while attempting to have children. In a phase II trial, it significantly reduced cumulative Gad+ lesions by 61%. Laquinimod suppresses the development of EAE in murine models and shifts cytokine balance from Th1 to Th2, and in phase II trials, it significantly reduced the cumulative number of Gad+ lesions by 40%. Cladribine, a purine nucleoside analog prodrug, is a selective T lymphocyte-depleting agent via its activation by deoxycytidine kinase, which is present in high levels in T-cells. It significantly reduced GAD+ lesions by 90% and relapse rate by 32%, compared with placebo, in a phase II trial.

Although early results with the new small-molecule oral agents for MS are certainly encouraging, they await verification from phase III trials. Unfortunately, these large studies are designed with placebo-controls; consequently, there may not be a sufficiently large patient pool who are willing to accept the risk of placebo to fully enroll all studies. Finally, issues such as the best use of these new drugs—whether as monotherapy, combination therapy, and/or induction therapy—remain to be explored.

Suggested Readings

Kappos L, Antel J, Comi G, et al. Oral fingolimod (FTY720) for relapsing multiple sclerosis. *N Engl J Med*. 2006;355:1124-1140.

O'Connor PW, Li D, Freedman MS, et al. A phase II study of the safety and efficacy of teriflunomide in multiple sclerosis with relapses. *Neurology*. 2006;66:894-900.

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Controversies in MS

Mark S. Freedman, HSBc, MSc, MD

Among the important outstanding questions in the field of multiple sclerosis (MS) are whether to treat or not to treat clinically isolated syndrome (CIS), how to choose a therapy, how to identify the suboptimal responder, how long to treat, and the role, if any, of combination therapy. Evidence is accumulating from a variety of studies demonstrating that early treatment results in benefits that cannot be regained by beginning therapy at a later point. Three studies in particular—CHAMPS, ETOMS, and BENEFIT—have shown that administering interferon beta to patients with CIS delays the time to a second attack and reduces MRI lesions. In addition, treatment of CIS with high-dose, high-frequency interferon beta also delays disability. However, while answers to the question of whether or not to treat CIS are becoming clear, determining specific treatment based on current clinical trial data is more difficult. In comparing the relative efficacy of different agents, direct head-to-head trials are obviously the best. Unfortunately, not all agents are compared against all other options in head-to-head trials. Since trials differ in terms of their patient populations, study designs, and placebo results, simply comparing results across trials may lead to erroneous conclusions. However, results of different trials can be compared if these results are converted into a common measure of effectiveness, such as the number needed to treat (NNT). NNT is the number of patients needed to receive a treatment over a set time period in order for one patient not to experience one outcome event, such as relapse, progression, or death. Recently, a new model was developed to help detect suboptimal response based on the level of concern for considering treatment modification. Level of concern can be determined based on various outcomes, including relapse, progression, or MRI changes. When this model was applied to year 1 of PRISM-4 treated patients, 89% of the medium/high concern patients had >1 relapse in years 2 to 4. Use of this model should facilitate the detection of suboptimal response and the need to consider alternate therapies. Finally, the issue of combination therapy—when, with what, and whether combination regimens are safe—is still unclear. Many agents have been explored, but most studies have been either uncontrolled or observational.

Suggested Readings

Comi G, Filippi M, Barkhof F, et al. Effect of early interferon treatment on conversion to definite multiple sclerosis: a randomised study. *Lancet*. 2001;357:1576-1582.

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Kappos L, Polman CH, Freedman MS, et al. Treatment with interferon beta-1b delays conversion to clinically definite and McDonald MS in patients with clinically isolated syndromes. *Neurology*. 2006;67:1242-1249.

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This ***free*** web-based curriculum presents the latest scientific developments, information on current and emerging therapies, and expert insights to help busy ***neurologists, nurses, and pharmacists*** improve outcomes in their patients with MS. Topics include:

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- Pathophysiology of MS
  - — Understanding MS and recognizing multiple forms of MS pathology
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