MS Academia
Multiple sclerosis advanced course
9 September 2014 - Boston, USA
Dear participant,

A warm welcome to all attending the "MS Academia - Multiple sclerosis advanced course".
I would like to inform you that as of 28 April 2014 the name of our Foundation changed to EXCEMED - Excellence in Medical Education. The name change will not impact your registration status in this or any other Foundation event.

This transition marks an exciting point in the evolution of the Foundation. We are proud to have provided world-class education to thousands of healthcare professionals over the past four decades - as a result, the Foundation has become synonymous with delivery excellence and high-impact CME.

As we further develop our scientific and geographical presence it is important to us that our name accurately reflects the independent nature of the education we provide; EXCEMED symbolises our enduring mission to support the best possible outcomes for patients through the medical education we offer. We take pride in our complete dedication to the provision of CME - it is our sole focus and our passion.

I wish you an inspiring and successful learning experience here in Boston.

Yours sincerely,

Rachel Clark
CEO, EXCEMED
General information

Venue
This live educational course takes place at the:
Hyatt Regency Boston Hotel
One Avenue de Lafayette
Boston, Massachusetts, USA, 02111
Phone: +1 617 912 1234

Language
The official language of this live educational course is English.

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EXCEMED live educational course:

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Aim
Multiple sclerosis (MS) is a multifaceted neurological disorder whose management requires a multidisciplinary team of highly specialised health professionals. The availability of new and sophisticated diagnostic tools and the discovery of new treatments has made daily clinical practice even more challenging for physicians involved in MS patient management. Tailoring the treatment to individual patient needs and establishing the right time to start therapy or to switch from traditional first-line disease-modifying therapies to other first- or second-line therapies are the biggest issues. The goal of this learning activity is to update participants about MS pathogenesis and diagnostic criteria and to provide a comprehensive overview of past and future disease-modifying therapies. In addition, the learner will be taught about strategies for symptomatic and rehabilitative care which have proven to be a necessity in overall MS management. This will enable emerging knowledge to be integrated with clinical practice.

Learning objectives
By attending this live educational course learners will be able to:

- Analyze genetic and environmental factors in the pathogenesis of multiple sclerosis to facilitate effective patient and family education
- Integrate clinical, neurophysiological, and MRI findings into the accurate diagnosis of multiple sclerosis and the exclusion of MS mimickers
- Incorporate information regarding the risks and benefits of currently available drugs for multiple sclerosis into treatment decisions
- Include symptomatic management of multiple sclerosis into the treatment paradigm of comprehensive management throughout the spectrum of the disease
- Recognize the contribution of rehabilitation services to overall wellness in MS and include when appropriate.

Target audience
This programme is appropriate for neurologists who specialize in MS as well as other clinicians with a special interest or focus on this disease.
Accreditation/Credit designation

This live activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education through the joint providership of the Consortium of Multiple Sclerosis Center (CMSC) and EXCEMED – Excellence in Medical Education. The CMSC is accredited by the ACCME to provide continuing medical education for physicians.

The CMSC designates this live activity for a maximum of 8.0 AMA PRA Category 1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

EXCEMED adheres to the principles of the Good CME Practice Group (gCMEp).
Scientific organisers

Giancarlo Comi  
Department of Neurology  
Institute of Experimental Neurology  
Vita-Salute San Raffaele University  
Milan, Italy

Hans-Peter Hartung  
Department of Neurology  
Heinrich-Heine-University  
Dusseldorf, Germany

Fred D. Lublin  
Corinne Goldsmith Dickinson Center  
for Multiple Sclerosis  
Mount Sinai School of Medicine  
New York, NY, USA

This live educational course in endorsed by ACTRIMS  
(Americas Committee for Treatment and Research in  
Multiple Sclerosis).

This live educational course is endorsed by ECTRIMS  
(European Committee for Treatment and Research In  
Multiple Sclerosis).

We value your opinion!

We are continually trying to develop and improve our educational initiatives to provide you with cutting-edge learning activities. During this live educational event you will be asked to answer a real-time survey and prior to this educational event and after you will be receiving an online survey to help us to better tailor our future educational initiatives.

Thank you for participating!
Faculty members

Alberto Ascherio  
Department of Epidemiology and Nutrition  
Harvard School of Public Health  
Harvard Medical School  
Boston, MA, USA

Amit Bar-Or  
Department of Neurology and Neurosurgery  
Montreal Neurological Institute  
Neurology, Microbiology and Immunology at McGill University  
Montreal, Canada

Wolfgang Brück  
Department of Neuropathology  
University Medical Center Göttingen  
Georg-August University  
Göttingen, Germany

Giancarlo Comi  
Department of Neurology  
Institute of Experimental Neurology  
Vita-Salute San Raffaele University  
Milan, Italy

Mark S. Freedman  
University of Ottawa and the Ottawa Hospital Research Institute  
Ottawa, Ontario, Canada

Gavin Giovannoni  
Centre for Neuroscience & Trauma, Blizard Institute  
Barts and The London School of Medicine and Dentistry  
Queen Mary, University of London  
London, UK

Hans-Peter Hartung  
Department of Neurology  
Heinrich-Heine-University and Center for Neuropsychiatry  
University Hospital and LVR Klinikum  
Düsseldorf, Germany

Jan Hillert  
Department of Clinical Neuroscience  
Karolinska Institutet  
Stockholm, Sweden

Letizia Leocani  
Institute of Experimental Neurology  
University Vita-Salute IRCCS  
San Raffaele Hospital  
Milan, Italy

Fred D. Lublin  
Corinne Goldsmith Dickinson Center for Multiple Sclerosis  
Icahn School of Medicine at Mount Sinai  
New York, NY, USA

Xavier Montalban  
Multiple Sclerosis Centre of Catalonia (Cemcat)  
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Vall d’Hebron University Hospital  
Barcelona, Spain

Maria Assunta Rocca  
Neuroimaging Research Unit  
Institute of Experimental Neurology  
Division of Neuroscience  
San Raffaele Scientific Institute  
Vita-Salute San Raffaele University  
Milan, Italy

Alan J. Thompson  
Department of Brain Repair and Rehabilitation  
Institute of Neurology University College London  
National Hospital for Neurology and Neurosurgery  
London, UK

Mar Tintoré  
Multiple Sclerosis Centre of Catalonia (Cemcat)  
Neurology-Neuroimmunology Department  
Vall d’Hebron University Hospital  
Barcelona, Spain
Scientific programme
Tuesday, 9 September 2014

8.15   EXCEMED opening

**Session I**  Etiology and Pathogenesis

**Chairs:** H.P. Hartung [Germany] - F.D. Lublin [USA]

- **8.30** L1: MS: diagnosis and prognosis
  X. Montalban [Spain]

- **9.00** L2: Genes
  J. Hillert [Sweden]

- **9.30** L3: Environment and nutrition
  A. Ascherio [USA]

- **10.00** L4: Immunopathogenesis
  H.P. Hartung [Germany]

  Revisiting real-time survey

- **10.35** Coffee break

**Session II**  Diagnosis

**Chairs:** G. Comi [Italy] - F.D. Lublin [USA]

- **11.00** L5: Neurophysiology in diagnosis and monitoring of MS
  L. Leocani [Italy]

- **11.30** L6: MRI in diagnosis and monitoring of MS
  M.A. Rocca [Italy]

- **12.00** CC1: Diagnosis and differential diagnosis
  M. Tintoré [Spain]

- **12.30** L7: Pathology
  W. Brück (Germany)

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- **13.05** Working Lunch

**Session III**  Treatment

**Chairs:** G. Comi [Italy] - H.P. Hartung [Germany]

- **14.00** L8: Symptomatic treatment
  F.D. Lublin [USA]

- **14.30** L9: Rehabilitation challenges and new approaches in MS
  A.J. Thompson [UK]

- **15.00** L10: Current disease modifying drugs: evaluating the evidence
  M.S. Freedman [Canada]

- **15.30** L11: Safety issues
  G. Giovannoni [UK]

- **16.00** Coffee break

- **16.25** L12: Treatment individualization and monitoring
  G. Comi [Italy]

- **16.55** L13: Future therapies
  A. Bar-Or [Canada]

- **17.25** PD: Treatment in Practice - Panel discussion
  G. Comi [Italy]
  M.S. Freedman [Canada]
  G. Giovannoni [UK]
  F. Lublin [USA]

  Revisiting real-time survey

- **18.00** Concluding remarks and end of the meeting

**Legend:**  **L** : Lecture;  **CC** : Clinical cases;  **PD** : Panel discussion
Biographies
Alberto Ascherio, MD, DrPH, is a Professor of Epidemiology and Nutrition at the Harvard School of Public Health and a Professor of Medicine at the Harvard Medical School. Dr. Ascherio trained in internal medicine at the University of Milan, and subsequently practiced medicine and public health in Latin America and Africa. He completed his doctoral degree in epidemiology at the Harvard School of Public Health. His research is primarily devoted to finding the causes of multiple sclerosis (MS), Parkinson’s disease (PD), and amyotrophic lateral sclerosis (ALS). Since 1997, he has directed the investigation of neurodegenerative diseases in several large cohorts. Among the most notable discoveries to which he has contributed are the key roles of infection with the Epstein-Barr virus, vitamin D insufficiency, and cigarette smoking as risk factors for MS, the importance of vitamin D status as a determinant of MS progression, the role of caffeine consumption and urate as negative risk factors for PD and urate elevation as a promising therapeutic strategy, and the identification of positive and negative environmental risk factors for ALS.

Amit Bar-Or is a neurologist and neuroimmunologist at the Montreal Neurological Institute (MNI), McGill University. His laboratory studies basic principles of immune-regulation, immune-neural interaction and neural-glial interaction, and roles in physiologic processes, inflammatory injury and repair in the human central nervous system. Dr. Bar-Or’s clinical focus is MS and he is currently the President of the Canadian Consortium of MS Clinics. He also serves as Director, Experimental Therapeutics Program and Scientific Director, Clinical Research Unit at the MNI. Dr. Bar-Or coordinates a number of multi-center national and international translational research initiatives. An overarching theme is translation of basic lab discoveries towards development and understanding of novel experimental therapies and biomarkers for patients with autoimmune and neurological diseases. Dr. Bar-Or serves on the several journal editorial boards and serves on the scientific/advisory boards of the Guthy-Jackson Greater-Good Foundation (NMO research); the Accelerated Cure Project; the ACTRIMS, ISNI and FOCIS organizations; and as Speaker of the Scientific Advisory, German National MS/Neuroimmunology Kompetenz Network. Following undergraduate work in biopsychology at McMaster University, Dr. Bar-Or received his medical degree cum laude from McGill University, then pursued Neurology residency and Fellowship training in Neuroimmunology at Harvard University where he also completed the Harvard/MIT Clinical Investigator Training Program (CITP).
Prof. Dr. Wolfgang Brück is head of the Department of Neuropathology at the University Medical Center Göttingen, Germany. His research focuses on the structural and immunopathological features of multiple sclerosis (MS) lesions, mainly focusing on mechanisms of degeneration and regeneration in MS lesions. The definition of different immunopathological subtypes of MS has been one of the most interesting research topics pursued in the last years. These studies in human tissue are paralleled by experimental studies in animal models of MS including autoimmune models in rodents and non-human primates as well as rodent models of toxic demyelination/remyelination.

Giancarlo Comi received a degree in medicine in 1973 and a neurological certification in 1977, both from Milan University. He joined the Department of Neurology, Scientific Institute San Raffaele, Milan University, in 1974 as a Clinical Assistant and in 1988 was appointed Assistant Professor in Clinical Neurophysiology of the same University. Currently he is Professor of Neurology, Chairman of the Department of Neurology, and Director of the Institute of Experimental Neurology, at Vita-Salute San Raffaele University, Scientific Institute San Raffaele, Milan. His fields of interest are principally directed towards the study of the pathophysiology and treatment of multiple sclerosis. Professor Comi has authored and co-authored more than 800 articles in peer-reviewed journals, and edited several books. He has a long-standing involvement as an active member of steering committees and advisory boards of many international clinical trials, mainly in the field of multiple sclerosis. He is currently the President of the European Charcot Foundation (ECF) and member of the Board of Administration of the Italian Multiple Sclerosis Foundation and the Scientific Committee of the Italian Multiple Sclerosis Association. Professor Comi has also served as President of the European Neurology Society and the Italian Society of Clinical Neurophysiology. He is currently the President of the Italian Society of Neurology for the period of 2012-2014. In the past year, he has received the Romanian Society of Neurology honorary award “Gh. Marinescu” and been awarded honorary membership of the Russian Neurological Academic Society. He currently sits on the executive boards of various scientific associations and in the editorial boards of Clinical Investigation, European Journal of Neurology, Multiple Sclerosis and is the Associate Editor of the Neurological Sciences.
Biographies

Mark S. Freedman  
University of Ottawa and  
the Ottawa Hospital Research Institute  
Ottawa, Ontario, Canada

Mark Freedman is Professor of Medicine (Neurology) at the University of Ottawa, Senior Scientist at the Ottawa Hospital Research Institute and Director of the Multiple Sclerosis Research Unit at the Ottawa Hospital-General Campus. His extensive research includes molecular neurochemistry, cellular immunology, and clinical studies in MS. His basic science interest concerns immune mechanisms of damage in MS, with a particular interest in the role of the innate immune system such as gamma-delta T-cells. His main clinical interests are cell-based therapies for MS. He was the lead investigator of the Canadian Bone Marrow Transplant Study in MS and he co-heads an international study of mesenchymal stem cells for the treatment of MS. He is the current Treasurer of ACTRIMS.

Gavin Giovannoni  
Centre for Neuroscience & Trauma, Blizard Institute  
Barts and The London School of Medicine and Dentistry  
Queen Mary, University of London  
London, UK

Gavin Giovannoni was appointed to the Chair of Neurology, Blizard Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London and the Department of Neurology, Barts and The London NHS Trust in November 2006. In September 2008 he took over as the Neuroscience and Trauma Centre Lead in the Blizard Institute. Gavin did his undergraduate medical training at the University of the Witwatersrand, South Africa, where he graduated cum laude in 1987. He moved to the Institute of Neurology, University College, Queen Square, London in 1993 after completing his specialist training in neurology in South Africa. After three years as a clinical research fellow, under Professor Ed Thompson, and then two years as the Scarfe Lecturer, working for Professor W. Ian McDonald, he was awarded a PhD in immunology from the University of London in 1998. He was appointed as a Clinical Senior Lecturer, Royal Free and University College Medical School, in 1998 and moved back to Institute of Neurology, Queen Square in 1999. He was promoted to Reader in Neuroimmunology in 2004. His clinical interests are multiple sclerosis and other inflammatory disorders of the central nervous system. He is particularly interested in clinical issues related to optimising MS disease modifying therapies. His current research is focused on Epstein Barr virus as a possible cause of multiple sclerosis, defining the “multiple sclerosis endophenotype”, multiple sclerosis related neurodegeneration, multiple sclerosis biomarker discovery, multiple sclerosis clinical outcomes and immune tolerance strategies. His team focus on translational research and therefore have an active clinical trial programme.
Hans-Peter Hartung
Department of Neurology, Heinrich-Heine-University and
Center for Neuropsychiatry, University Hospital and LVR Klinikum
Düsseldorf, Germany

Hans-Peter Hartung is Professor and Chairman of the Department of Neurology, Heinrich-Heine-Universität, Düsseldorf. Following his MD in 1980, he undertook research fellowships in immunology and neuroimmunology in Germany. In 2001, he took up his current position. His research interests are in experimental and clinical neuroimmunology, pathogenesis of and experimental therapies for MS, Guillain-Barré syndrome, CIDP, and neuromuscular diseases. Hans-Peter Hartung heads a 64 bed university department with clinical and research groups including stroke, movement disorders, magnetoencephalography, MS, Neuro-HIV, and neuromuscular diseases. He is also co-director of the Center for Neuropsychiatry, UKD LVR Klinikum Düsseldorf and head of its division of neurology, a 36 bed unit. He is a member of a number of societies, a Fellow of the American Academy of Neurology, American Neurological Association, former board member of the European Neurological Society, Fellow of the Royal College of Physicians in the UK and Honorary member of the All-Russian Society of Neurologists. He reviews publications and is a member of editorial boards covering issues including MS, research, and neurology and neuroimmunology in general. He is involved with a number of international multicentre trials of treatments for MS, Guillain-Barré Syndrome and CIDP. He has published more than 800 peer-reviewed articles on the pathogenesis and treatment of neuroimmunological disorders, has written nine books and some hundred book chapters.

Jan Hillert
Department of Clinical Neuroscience
Karolinska Institutet
Stockholm, Sweden

Jan Hillert has been Professor of Neurology at the Karolinska Institute, Stockholm, Sweden, since 2001, and in 2010 was appointed Chairman of the Department of Clinical Neuroscience. Professor Hillert has led a multiple sclerosis (MS) clinic for over 10 years and is founding chair of the Swedish Multiple Sclerosis Registry, which contains information on 15,000 MS patients. He is actively engaged in several MS clinical trials and has published 240 peer-reviewed papers. Professor Hillert’s research primarily focuses on the genetic aspects of MS and has contributed to the discovery of several MS genes. Additional research interests include immunology and treatment aspects of MS, including treatment-induced antibodies. Current research efforts focus on translational epidemiology, integrating clinical, genetic, environmental, and public registry data both nationally and internationally.
Letizia Leocani is Supervisor of Experimental Neurophysiology Laboratory at the Scientific Institute Hospital San Raffaele, Milan. After the Degree in Medicine at the State University of Milan, Letizia Leocani completed a PhD in Human Physiology and specialized in Neurology at the same University. She was Research Fellow at the National Institutes of Health (Bethesda, USA). She has been the Secretary and currently is a Board member of the Italian Society of Psychophysiology. She has been a Board member and International Delegate of the Italian Society of Clinical Neurophysiology and is currently the national representative of UEMS—Clinical Neurophysiology Section. Her main areas of scientific interest concern the electrophysiological study of central nervous system, with particular reference to motor and cognitive functions and to neurophysiological and psychophysiological research methods (functional neuroimaging with advanced analysis of electroencephalography and evoked potentials, transcranial magnetic stimulation).

Fred D. Lublin, M.D. 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. 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 Multiple Sclerosis and the National Multiple Sclerosis Society’s Research Programs Advisory Committee. He is a member of the National MS Society National Board of Directors and their medical advisory board. He is 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 using data from a survey of the international MS community. 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. 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 is a Co-Chief Editor of the new journal Multiple Sclerosis and Related Disorders. Dr. Lublin has published numerous scientific articles and belongs to 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 is the Principal Investigator of the NIH-sponsored multicenter Combination Therapy study in Multiple Sclerosis.
Xavier Montalban
Multiple Sclerosis Centre of Catalonia (Cemcat)
Neurology-Neuroimmunology Department
Vall d’Hebron University Hospital
Barcelona, Spain

Professor Montalban is Vice President of the Multiple Sclerosis Foundation, and sits on the advisory board and the scientific committee of the Multiple Sclerosis International Federation and the European Charcot Foundation. Since 2003, he has been a member of the advisory committee on clinical trials of new agents of the National Multiple Sclerosis Society in the United States. He has been a member of ECTRIMS since 2009 and is currently Vice President. His current research interests include immune mechanisms in MS, cognitive dysfunction in MS, new intervention strategies, genetic characterization and pharmacogenomics of treatment response and prognostic factors of MS. He has participated both in the design and execution of several phase II and phase III clinical trials, and is member of several safety and steering committees.

Maria Assunta Rocca
Neuroimaging Research Unit, Institute of Experimental Neurology
Division of Neuroscience, San Raffaele Scientific Institute
Vita-Salute San Raffaele University
Milan, Italy

Maria A. Rocca took her Graduation in Medicine in 1996 and her Post-Degree Graduation in Neurology in 2002. Dr. Rocca is currently Head of the “Neuroimaging of CNS White Matter Unit”, Department of Neurology, Institute of Experimental Neurology, Scientific Institute Ospedale San Raffaele, Milan, Italy. Her activity is mainly focused on the application of structural and functional MR-based techniques to improve the understanding of central nervous system function and dysfunction in healthy individuals and diseased people, particularly patients with multiple sclerosis (MS) and other white matter disorders. Dr. Rocca is currently conducting and coordinating several national and international projects in adult and paediatric populations. She is also extensively applying advanced methods of analysis in an attempt to improve the understanding of the role of the brain’s functional and structural plasticity in the different phases of MS, and the influence of pharmacological and rehabilitative interventions on brain reorganization. She is a member of various national and international scientific societies and, in some of them, covers or is covering institutional roles (MAGNIMS, ENS, Neuroimaging Study Group of the Italian Neurological Society, AMPC of the ISMRM). She has also coordinated the MRI acquisition and analysis of several large-scale international MRI-monitored trials of MS. Dr. Rocca is author or co-author of more than 306 papers published in peer-reviewed journals and of 36 book chapters. She is also a reviewer of several international scientific journals and for many governmental organisations and private foundations. She is the recipient of several national and international awards for her scientific work and her roles as a speaker and/or chairperson at more than 250 international congresses. Dr. Rocca is a Non-Tenured Professor at Università Vita-Salute San Raffaele, Milan, Italy.
Biographies

Alan J. Thompson

Department of Brain Repair and Rehabilitation  
Institute of Neurology University College London  
National Hospital for Neurology and Neurosurgery  
London, UK

Professor Alan Thompson is Dean of the Faculty of Brain Sciences at University College London, Garfield Weston Professor of Clinical Neurology and Neurorehabilitation at the UCL Institute of Neurology, a consultant neurologist at the National Hospital for Neurology and Neurosurgery, Queen Square, and Chair of the Neuroscience Programme at the UCLP Academic Health Sciences Centre. His main area of expertise is in demyelinating disease, particularly the diagnosis, evaluation, and management of multiple sclerosis (MS), focusing on the pathological mechanisms that underpin neurological disability and recovery using structural and functional imaging. He has published extensively in high-impact peer-reviewed journals, and has an H-index of 93. Professor Thompson is chair of the Scientific Committee of the International Progressive MS Alliance, Chairman of the International Medical and Scientific Board of the Multiple Sclerosis International Federation (MSIF), a Senior Investigator for the National Institute for Health Research, Editor-in-Chief for Multiple Sclerosis Journal, and a Guarantor of Brain. He received his undergraduate and postgraduate degrees from Trinity College Dublin, and an honorary doctorate from Hasselt University, Belgium.

Mar Tintoré

Multiple Sclerosis Centre of Catalonia (Cemcat)  
Neurology-Neuroimmunology Department  
Vall d’Hebron University Hospital  
Barcelona, Spain

Dr. Mar Tintoré serves as a neurologist at the Neurology/Neuroimmunology Department, MS Centre of Catalonia (Cemcat), Hospital Vall d’Hebron (Barcelona). The unit follows a patient base of over 4000 persons with MS and receives some 600 new cases for investigation, diagnosis and therapy. Weekly, the unit sees about 120 patients, 20 of whom are new referrals. The Cemcat was created with the added aim to conduct clinical and basic research on MS in aid of the persons living with MS. At present, a number of both phase II, III and IV clinical trials are being conducted. Dr. Tintoré’s main research line at the UNIC is based on first presentations of demyelinating events, magnetic resonance, immunological aspects and MS treatment rendering a number of internationally renowned publications. Currently, Dr. Tintoré is involved in the furthering of the EU concerted action by the acronym MAGNIMS, involving many European countries, to study magnetic resonance in clinically isolated syndromes (CIS) and early MS. Below is a sample of Dr. Tintoré’s publication record of over 100 publications in national and international peer-reviewed journals. Finally, Dr. Tintoré is a reviewer for national and international journals and national research support and funding agencies.
EXCEMED adheres to guidelines of the European Accreditation Council for Continuing Medical Education (EACCME®) and all other professional organizations, as applicable, which state that programmes awarding continuing education credits must be balanced, independent, objective, and scientifically rigorous. CMSC adheres to accreditation requirements and standards of the Accreditation Council for Continuing Medical Education (ACCME). Investigative and other uses for pharmaceutical agents, medical devices, and other products (other than those uses indicated in approved product labeling/package insert for the product) may be presented in the programme (which may reflect clinical experience, the professional literature or other clinical sources known to the presenter). All persons that have influenced the content of this CME activity are required to provide CMSC and EXCEMED with information about relationships with pharmaceutical or medical equipment companies that may have relevance to their lectures for the purpose of identification and resolution of any potential conflict of interest. Per ACCME standards, this disclosure information is provided to participants. This policy is not intended to exclude faculty who have relationships with such companies; it is intended to insure fair balance by resolving any conflicts and to inform participants of any potential conflicts so that participants may form their own judgements, based on full disclosure of the facts. Further, all opinions and recommendations presented during the programme and all programme-related materials neither imply an endorsement nor a recommendation on the part of EXCEMED or CMSC. All presentations represent solely the independent views of the presenters/authors.

The following faculty, planners and reviewers provided information regarding relevant commercial relationships and/or discussions of investigational or non-EMEA/FDA approved (off-label) uses of drugs:

**Alberto Ascherio**
Declared no potential conflict of interest.

**Amit Bar-Or**
Declared to have participated as a speaker at meetings sponsored by, received consulting fees and/or received grant support from: Amplimmune, Bayhill Therapeutics, Berlex/Bayer, Biogen Idec, Biogenix, Eli-Lilly, Genentech, GlaxoSmithKline, Guthy-Jackson/GGF, Merck/EMD Serono, Medimmune, Mitsubishi Pharma, Novartis, Ono Pharma, Receptos, Roche, Sanofi-Genzyme, Teva Neuroscience, Wyeth.

**Wolfgang Brück**
Declared receipt of grants and contracts from Teva Pharmaceuticals, Biogen Idec, Novartis, Roche. He declared to have received honoraria or consultation fees from Teva Pharmaceuticals, Novartis, Biogen Idec, Bayer, Merck-Serono, Genzyme. He declared to be a member of the company advisory board, board of directors or other similar group in Teva Pharmaceuticals, Novartis, and Genzyme.

**Giancarlo Comi**
Declared receipt of consulting fees from Novartis, Teva, Sanofi, Genzyme, Merck, Biogen, Baye, Almirall, Chugai, Receptos. He declared to have received research grants and funds from Novartis, Teva, Sanofi, Genzyme, Merck, Biogen, Almirall, Chugai, Receptos, Actelion.

**Mark S. Freedman**
Declared to have received grant and contracts from Biogen Idec, EMD Canada, Genzyme, Novartis, Opexa, Teva Canada Innovation. He declared to be a member of a company advisory board, board of directors or other similar groups at Biogen Idec, EMD Canada, Genzyme, Novartis and Opexa. He declares he participated in a company sponsored speaker’s bureau: Genzyme.

**Gavin Giovannoni**
Declared to be a member of the steering committee of: AbbVie, Biogen Idec, Novartis, Teva, Roche. He declared to have received consulting fees for advisory board meeting from Biogen Idec, GW Pharma, Merck Serono, Novartis, Genzyme-Sanofi. He declarel also to have received other consultancy fees from Fiveprime, Ironwood, Sython BV, Vertex Pharmaceuticals. He declared the receipt of honoraria from Biogen Idec, Novartis, Genzyme-Sanofi. He declared to have been a clinical advisor in Canbex.

**Hans-Peter Hartung**
Declared to have received honoraria or consultation fees from Bayer Healthcare GmbH, Biogen Idec, GeNeuro, Genzyme, Hoffman-La Roche, Medimmune, Merck Serono, Novartis, Teva, Sanofi Aventis.

**Jan Hillert**
Declared to have received honoraria for serving on advisory boards for Biogen Idec and Novartis and speaker’s fees from Biogen Idec, Merck-Serono, Bayer-Schering, Teva and Sanofi-Aventis. He has served as P.I. for projects sponsored by, or received unrestricted research support from, Biogen Idec, Merck-Serono, TEVA, Novartis and Bayer-Schering. His MS research is funded by the Swedish Research Council.
Letizia Leocani Declared no potential conflict of interest.

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Abstracts
Abstract not in hand at the time of printing.
There has been remarkable success within the past few years in identifying the genes of complex diseases such as multiple sclerosis (MS). Advances in the methodology behind combining large clinical materials with high thru-put genotyping techniques are responsible for this growing insight. As a result, we now have a list of over 200 genes or chromosomal loci which very strong evidence indicates an influence in determining the risk for an individual developing MS. The prime objective with risk gene identification is to increase understanding of the early triggering events in MS pathogenesis. The new list of MS genes may eventually prove to be immensely important as clues for disease mechanisms. In brief, most of the new genes are of clear importance for inflammation, thus supporting the hypothesis that MS is primarily a disease with autoimmune features. This presentation will briefly address which genes these are and how we came to identify them.

The presentation will also cover the current level of understanding and potential usefulness of genetic markers in diagnosis, prognosis and treatment decisions - specifically, the extent to which these or similar markers are associated with characteristics other than onset of disease. In brief, we have a considerable way to go before genetics will add substantially to the diagnostic accuracy in the MS clinic. Likewise, genetic markers have so far not allowed us to predict the course of our patients, but may be of some use if analysed in concert with other factors. Finally, there are already some examples of genetic factors influencing the response to treatment in autoimmune disorders, including MS.

In summary, the genomics mission in MS, expected to be completed within 5-10 years, has already proven to be a success. Hopefully this will eventually translate into practical outcomes for patients and neurologists.
Main objective
To provide an update on non-genetic determinants of MS risk.

Topics
Cigarette smoking, EBV infection & history of mononucleosis, childhood obesity, and vitamin D insufficiency.

Critical issues
1. While genetic susceptibility explains the clustering of MS cases within families, the changes in MS risk that occur with migration can only be explained by changes in the environment.
2. The environmental determinants of MS risk include cigarette smoking, EBV infection & history of mononucleosis, childhood obesity, and vitamin D insufficiency.
3. The increased risk of MS among smokers is noteworthy because it contributes to explain the increasing female to male gender ratio in MS.
4. The strongest known risk factor is infection with the Epstein-Barr virus (EBV). MS is extremely rare in individuals who are not infected with EBV, but it has been shown in a longitudinal study that their MS risk increases sharply following EBV infection. As compared with uninfected individuals, the hazard of developing MS is at least 10 folds higher among individuals infected with EBV in childhood and over 20 folds higher among individuals infected in adolescence or later in life. Although the mechanisms underlying this association remain unclear, these data provide strong evidence of a causal relation between EBV infection and MS risk. Some aspects of the epidemiology of MS, however, are not explained by EBV, suggesting that either there are different EBV strains, with different propensity to cause MS, or other factors are also involved.
5. An increased risk of MS in individuals with vitamin D insufficiency has been proposed to explain the strong latitude gradient in MS prevalence. Results of case-control studies that relied on prevalent MS cases and recall of past exposure to sunlight and vitamin D intake have been mixed and potentially affected by selection and recall biases. Three longitudinal studies have been so far completed. In the first, based on assessment of vitamin D intake from diet and supplements, risk of MS was found to be 30% lower among women in the highest quintile as compared to those in the lowest quintile. In the second study, conducted among young adults in the US Army and Navy, vitamin D status was assessed by averaging multiple season-adjusted measures of 25(OH) vitamin D. During an average of 5-years of follow-up, MS risk among healthy young adults with high serum levels of 25(OH) vitamin D (> 100 nmol/L) was about 60% lower than in individuals of the same age and sex with low serum 25(OH)D levels. The third study, recently published, confirmed prospectively an inverse association between serum 25(OH)D levels and MS risk among Swedish women. Combined, these results support the existence of a causal effect of vitamin D on MS risk.
6. The importance of vitamin D is corroborated, albeit indirectly, by observations that childhood obesity is a risk factor for both vitamin D insufficiency and MS.
7. Further, vitamin D insufficiency early in the course of MS is a strong risk factor for MS activity and progression. In a recent study, a 50 nmol/L increase in serum 25(OH)D levels early in the disease course predicted a 57% lower rate of new active lesions and a 41% lower yearly loss in brain volume over 5 years of follow-up.

Conclusions
Until a vaccine or other effective intervention is found to reduce the increased MS risk associated with EBV infection, preventive measures should focus on avoidance of smoking, childhood obesity, and correction of vitamin D insufficiency. The latter could also contribute to improve the prognosis of individuals with MS.
The pathogenesis of MS involves an intricate interplay between genetic, immune and environmental factors. GWAS studies conducted in large MS cohorts identified multiple genes conveying susceptibility to develop the disease which for the most part appear to be involved in T cell activation. These results are in line with observations in the time-honored experimental model EAE in which convincing proof for a pathogenic role of autoreactive myelin-directed T cell responses is available. A skewed immune repertoire may be decisively shaped by the gut microbiome and activation governed by pathogen associated molecules. B cells may either in synergy or in distinct subforms of MS also drive an autoimmune response directed against proteins contained in the myelin sheath. They could as antigen presenting cells induce T cell proliferation or upon differentiation into plasmablasts and plasma cells be the source of pathogenic autoantibodies. Continued B cell activation and sustained proliferation may occur compartmentalized particularly in the secondary progressive phase of the disease. A cognate aberrant T cell response results in parenchymal damage when lymphocytes access the CNS. Multiple molecular mechanisms are involved. Recent experimental evidence suggests that T cells are licensed in the lung to invade the CNS. Re-activation of immigrated T cells occurs when they recognise their antigen on local antigen presenters, predominantly microglia, in an appropriate inflammatory milieu. Then inflammatory cascades are set in motion involving cytokines, proteases, reactive oxygen and nitrogen species amongst others that culminate in damage to myelin and axons/neurons. Autoantibodies may be crucial in mediating demyelination. Innate immunity may be of particular importance when the disease transitions from the relapsing to the progressive phase. Whether axonal fallout, essentially determining permanent disability in MS, is a consequence of an overwhelming inflammatory response and represents collateral damage, or due to distinct immune responses to neuronal antigens remains elusive. In fact, the intensive search into the nature of the autoantigens has not yielded unequivocal results.

Current thoughts on the immunopathogenesis will be reviewed and open questions will be addressed in this lecture.

References:
In Multiple Sclerosis (MS), the underlying pathology may precede by years the clinical presentation. Demyelination and neurodegeneration lead to accumulation or progression of disability, although may be countered by functional reorganization, together with some level of remyelination and neuroregeneration. Indeed, early MS disease course is dependent on the balance between demyelination and remyelination, with the clinical manifestation determined by the degree of plasticity offsetting the effect of damage. Although the pathogenesis of demyelination has been well described, the cellular and molecular mechanisms of neurodegeneration are not fully understood. Among the major factors, ion channel expression and redistribution, together with neuroprotective pathways counteracting oxidative stress and mitochondrial dysfunction have been identified. Neurophysiological methods, mainly evoked potentials, are currently used for the assessment of functional consequences of demyelination, remyelination and axonal loss occurring in the course of the disease, as well as in pre-clinical testing. The functional information provided by evoked potentials accounts for their correlation with disease severity and point to their possible role as paraclinical measure for monitoring disease progression. In particular, they can help assessing the functional impact of the disease on central sensorimotor and cognitive networks affected by MS, and may reveal subclinical lesions. Furthermore, they also provide some prediction on the future evolution of disability, consistently with the hypothesis that early demyelination may prompt future neuronal loss, as shown in longitudinal studies. If further validated, neurophysiological methods may have a role in the early identification of patients who are more likely to develop future disability and for whom a closer clinical monitoring of treatment response is necessary. Finally, the possibility to demonstrate improved conduction through evoked potentials can represent a key feature in the assessment of efficacy of novel therapeutic approaches targeting remyelination.

References:
Measures derived from conventional magnetic resonance imaging (MRI), including the number of active lesions, as well as the overall burden of T2-hyperintense and T1-hypointense lesions, and brain volume, have clear advantages over clinical assessment, including that they are more objective and have an increased sensitivity to multiple sclerosis (MS) related changes. For these reasons, conventional MRI has been incorporated into the diagnostic workup of patients with clinically isolated syndromes who are at risk of developing MS, and it is always recommended in patients with definite MS to monitor the course of the disease. Even though no standardised guidelines exist, follow-up brain MRI is advised whenever new diagnostic questions arise or new neurological symptoms develop, especially if suggestive of comorbid conditions. Patients about to start a new treatment or to change treatment should undergo a brain MRI scan. This MRI scan should then be repeated after 6 and 12 months to assess the effectiveness of the treatment regimen. In addition, conventional MRI-derived end-points have been used as primary and secondary outcome measures for monitoring MS clinical trials. The rationale for using conventional MRI scans as surrogates for clinical outcomes is that the efficacy of a treatment in reducing relapses can be predicted at a trial level by its capacity to reduce active MRI lesions. In this context, the most widely used conventional MRI measures are those reflecting disease activity (new or enlarged T2 lesion counts, enhancing and new gadolinium-enhancing lesion counts, enhancing lesion volume measurement) and accumulated disease burden (T2 lesion load assessment). In the near future, it is likely that novel MR markers of MS evolution will be offered by non-conventional techniques and ultra-high field scanners.

References:
Diagnostic criteria for MS rely on the demonstration of CNS disease in space and time and in reasonable exclusion of other causes. Since McDonald 2001, in patients with a first attack, evidence of diagnosis for dissemination in space and time may be provided by MRI. The 2010 McDonald criteria selected the Magnims criteria for dissemination in space (DIS). DIS is defined as the presence of \( \geq 1 \) asymptomatic T2 lesion(s) in at least two of four locations considered characteristic for MS in previous MRI criteria: juxtacortical, periventricular, infratentorial and spinal cord. These criteria simplify the previous Barkhof criteria and highlight the importance of lesion location for MS diagnosis. Moreover, this new definition relies on T2 lesions only. Non-inclusion of gadolinium enhancing lesions seems appropriate since enhancing lesions per se provide information on disease activity and not on dissemination in space. For demonstration of dissemination in time (DIT), an MRI performed at any time demonstrating DIS and showing at least one or more asymptomatic gadolinium enhancing and non-enhancing lesion(s) (this being used as evidence for DIT) would be sufficient to diagnose MS. Although many studies have already shown the importance of CSF study in the diagnosis and differential diagnosis of MS, the presence of oligoclonal bands has not been included in the diagnosis algorithm. These criteria have been adapted to other populations such as patients with primary progressive MS or patients with paediatric MS. An overview of the past diagnostic criteria will also be performed as well as new directions for the future will be considered (intracortical lesions, 3 Teslas MRI, other). Clinical cases to illustrate differential diagnoses will be presented.
Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system which leads to focal destruction of myelin, acute axonal damage/loss of axons and reactive astrogliosis. The irreversible axonal loss is thought to be the major correlate of chronic disability in MS. MS has long time been considered a focal white matter disease, however, nowadays it is accepted that MS involves the entire central nervous system (CNS), including the grey matter and the normal-appearing white and gray matter.

The presentation discusses the pathological events occurring in these three compartments:

1. Focal white matter lesions: lesion characteristics/heterogeneity in early and progressive disease stages concerning the composition of the inflammatory infiltrate; extent of demyelination and remyelination; oligodendrocyte pathology; acute axonal damage and axonal loss.
2. Cortical demyelination: types of cortical lesions; consequences of demyelination for the neuronal compartment; remyelination in the cortex.
3. Normal appearing white and gray matter: diffuse inflammation and microglial activation; axonal damage and loss

The pathology in relation to different disease stages is discussed in detail.
In this exciting era of disease modifying therapies for MS, it is easy to overlook the importance of skilled, aggressive management of the patient’s symptoms. While disease modifying therapies are designed to alter the future disease course of MS, symptom management is designed to deal with the patient’s current conditions. Modern comprehensive care of patients with MS requires careful attention to both strategies. As multiple sclerosis can affect any part of the central nervous system, the symptoms that may result can be broad ranging and multiple. Some of the common symptoms that may need management include fatigue, spasticity, spasms, weakness, incoordination, impaired mobility, tremor, paroxysmal symptoms, bladder dysfunction, pain, cognitive impairment, sexual dysfunction, psychological and psychiatric problems. There are therapeutic strategies for treating each of these symptoms. Some, such as bladder dysfunction, have a number of successful therapies. Others, such as tremor and cognitive dysfunction are more difficult to manage. As a part of comprehensive MS care, one should take a holistic, multimodal view of therapy, taking into consideration all of the patient’s symptoms and other medical conditions. For example, a patient that is to be treated for depression, who also complains of fatigue, might do better with an activating antidepressant, rather than one that could sedate. Another example would be to consider utilizing an agent that has anti-cholinergic side effects in an individual who has a hyperactive bladder; and the reverse for someone who has a tendency to urinary retention. It is also very important to remember that our current disease modifying therapies and those in the pipeline have potential side effects and complications that require monitoring, a detailed understanding of any co-morbidities and potential interventions.

What is most important is to remember that comprehensive symptom management is a critically important aspect of all MS care, and all MS patients, from the very benign to the most malignant. Careful attention to each individual patient’s symptoms and the potential therapies for those symptoms will vastly improve the quality of life of our patients.
The philosophy underpinning rehabilitation is highly appropriate to the unpredictable and diverse needs of those affected by multiple sclerosis (MS). Some of the major challenges facing rehabilitation in MS include:

- Convincing the community that rehabilitation has a role in this variable unpredictable condition
- Measuring impact across all domains
- Demonstrating benefit
- Determining cost-benefit analysis (e.g. in vocational rehabilitation)
- Applying rehabilitation to more disabled patients with progressive MS

The key elements of this educational process, which seeks to increase ability, participation and autonomy, are well-suited to the management of the multiple symptoms inherent to this condition. Randomised controlled trials provide a reasonable evidence base supporting multi-disciplinary rehabilitation in out-patient and in-patient settings and this is supported by the Cochrane Collaboration. These studies are however limited by the evaluating tools utilised which often fail to incorporate the patient’s own perception of benefit. There is a need to develop better, more scientifically sound patient-related outcome measures (PROMS) and to apply newer measurement techniques such as Rasch analysis and item response theory. There is a need to target specific disabling symptoms such as spasticity, weakness and cognitive impairment and to improve approaches in vocational rehabilitation.

It is also important that we explore new approaches to rehabilitation including robotics and neuroplasticity. Recent studies targeting both MS and optic neuritis suggest a degree of plasticity which may compensate for impairment and indicate that the extent of response may influence recovery. A better understanding of plasticity could be invaluable in reducing impairment and provide an ideal target to guide and enhance the rehabilitation process.

This presentation will:
1. Outline the conceptual basis for Neurorehabilitation and its importance in achieving optimum quality of life in MS patients.
2. Evaluate the data concerning the effectiveness of Neurorehabilitation in MS.
3. Discuss some of the exciting new approaches which have the potential to push the boundaries and have an impact on restoration and repair.
The treatment of MS is becoming more complex, especially with the expanding number of available therapies for relapsing forms of MS. Perceived mechanism of action and benefit to risk profile are some of the main driving forces for enabling physicians to choose among therapies; however, it is often the clinical data supporting the efficacy that compels physicians to try and compare among the various therapies in order to form an opinion on “relative” efficacy. Despite the fact that patient populations, diagnostic definitions, frequency of neurological examinations and MRI studies, and statistical analysis differ widely among trials, it is especially the variable response of placebo groups that make it difficult to simply compare efficacy outcomes from various trials. A perfect example is to compare the same medication and the effect it achieved over a decade of various trials evolving to date; contemporary studies yield greater efficacy, yet medications have not changed. Evidence based approaches help to iron out some of these differences and concentrate on “absolute” efficacy, which can be reduced to a more conservative comparator, the “number needed to treat” or NNT. These NNT values are not perfect comparators either, since they may underestimate true treatment effects, especially when rates of the outcome measure become very small that overall differences between treatment and placebo groups is blurred. This is in fact the case with more recent trials, where relapse rates in the placebo group have fallen below 0.5 attacks per year and well below the treated relapse rates of yesteryear. The NNT now reflects not only the number of people requiring treatment for a period of time to prevent an event such as relapse, usually 2 years, but it also reflects the rarity of the event. Can NNT values to prevent a rarer event today be compared to those preventing the same but more common event 10 or more years ago? Though results of contemporary treatment trials provide statistically significant results, the magnitudes of the differences between treatments and placebo have become so small that it is difficult to understand their clinical meaningfulness.

To date, all studies examine activity measures considered independent of each other; i.e. patients having relapses need not also be having MRI activity or EDSS progression. Would it not make sense that a relapse leaving a patient with a higher EDSS and accompanied by new MRI lesions count more than one without either? Another way to assess the efficacy of medications is to examine if they increase the number of patients “free of detectable disease” compared to placebo or another treatment. The result would be a positive message in that a treatment would increase the likelihood of “no evidence of disease activity” (NEDA). Such an analysis need not assume that any outcome in particular [relapse, EDSS progression or MRI activity] is more important, but would consider that all are probably not good, so being free of all of them is therefore probably a good thing. In order to have “no evidence of disease activity (NEDA)”, a patient must have all 3: no relapses; no MRI activity; and no EDSS progression. One caveat from this approach is that many patients are in fact “NEDA” owing to their natural history, but that number would only be known if there is a placebo-comparator group. Many placebo patients in contemporary trials have in fact “NEDA”. Outside of trials such patients would be considered to be “false responders” to a medicine and there is no way of identifying them. Another problem with the NEDA approach is that any type of activity would render a patient not NEDA and this would be governed by the most frequent event, which undoubtedly is the MRI. Differences in the number of clinical or MRI assessments could easily skew results, since “the more you look – the more you find”. Nevertheless this type of analysis has been producing interesting results. One might consider the opposite approach (i.e. to count relapses only if the same individual had MRI activity AND EDSS progression) in order to count only the most meaningful of negative events. However, in that circumstance, the outcome is determined by the least frequent event, which would be EDSS progression, requiring a very large sample size to determine a treatment effect that is based on a very small segment of the study population.

Future trials focusing on outcome measures such as relapse rates will no doubt require many more patients to show what studies a decade or more ago did with a fraction of the patients. Still one should have an approach to compare agents based on known, validated outcome measures. Some of the more exploratory outcomes are of interest, but are not validated outcome measures, no matter how compelling they may be. For example, an agent that may show only modest effects on relapses, but marked effects on brain volume (atrophy) might be construed as powerful if one puts a lot of emphasis only on the MRI outcome. Alternatively, some treatments may have different mechanisms of action, and reducing relapses may reflect only a part of the benefit. It cannot simply be assumed that randomization to insure groups are equal in terms of their overall risk of having a relapse, also properly distributes patients based on their risk of losing brain volume. Groups need to first be selected based on known and perceived “risks of atrophy” before randomization. It is not enough to consider just the perceived benefits of an agent, without taking into account any risk of “harm” that might be taken in order to gain the benefit; a similar conservative measure of this is the “number needed to harm” or NNH. It is the true “benefit to risk” ratio that will undoubtedly take over as the mainstay for comparing contemporary and future treatments. One method could be to...
compare the "likelihood of help vs. harm" by simply calculating the NNT vs the NNH. However, as new agents with different properties loom for the treatment of MS, we are discovering that although the "benefits", based on validated outcome measures, can be comparable, the "harm" however is not and each new agent seems to bear its own new type of "harm".

Finally, all results from trials represent "group data" and there is no guarantee that any patient is apt to obtain the mean result of studies – some may do very well while others are affected minimally. It is for that reason that treatments must be "individualized" and each patient assessed to know whether any chosen treatment is in fact producing its desired effect.
Multiple sclerosis (MS) is the most common non-traumatic disabling condition to afflict young adults. Although the prognosis of MS is highly variable, given sufficient time the majority of people with MS will become disabled. In the case of established MS disease-modifying therapies the long-term impact of these therapies on MS prognosis is not fully defined, but appears promising. In the case of the newer therapies the short-term data is very promising. Despite this there is an emerging consensus that early highly-effective treatment, in the relapsing phase of the disease, will prevent or at least delay the progressive stage of the disease. The problem associated with the using highly-effective therapies, be they induction or escalation therapies, is that they come with greater known risks and undefined unknown risks. Chemotherapy induced premature ovarian failure and accelerated disease progression, steroid-induced osteoporosis and avascular necrosis, mitoxantrone-related leukaemia and cardiomyopathy, natalizumab-associated progressive multifocal leukoencephalopathy (PML), alemtuzumab-associated autoimmune diseases, opportunistic infections and possibly treatment-related malignancies, fingolimod associated PRES, macular oedema, cardiac conduction abnormalities and possibly sudden death. How do we balance the risks of these therapies with their potential long-term benefits? In this talk I will review the prognosis of MS and the rationale for treating early with highly effective therapies and provide strategies for de-risking these therapies for people with MS. In addition, the talk will focus on education and the role of the professional patient in helping make the right decision regarding individualised treatment plans.
Current disease-modifying therapies for multiple sclerosis (MS) include interferon (IFN) beta (subcutaneous [sc] and intramuscular [im]) glatiramer acetate, mitoxantrone, and natalizumab, are characterized by specific safety and efficacy profile. These therapies have demonstrated clear efficacy in clinical trials and in postmarketing studies; however the full response on long term is rare. This opens the requirement of alternative therapies in order to achieve the goal of obtaining full control of the disease. Fingolimod has been recently approved by Regulatory Authorities and other potential new treatments are in different phases of development. The availability of multiple therapeutic options permits the ambitious target of a full control of disease activity in multiple sclerosis. MS evolution is quite variable from patient to patient with possibility of a very aggressive course from the onset.

Early and accurate assessments may help to identify patients who require more aggressive therapeutic options. The definition of individual prognostic factor with the history of previous treatments will contribute to define the best candidate therapy for a given patient at a specific time of disease evolution. In the future, it may become possible to use also pharmacogenomic information to individualize treatment. Recent studies have confirmed the association between glypican 5 gene polymorphisms and response to IFN-beta treatment. Close monitoring of the response to treatment with clinical biomarkers will be fundamental in order to allow rapid shift from a treatment to another.

Patient adherence to prescribed treatment is hugely variable and can influence decision-making. An assessment of each patient’s benefit-to-risk preferences may also help to identify those patients who are willing to accept additional risks in exchange for potentially greater clinical efficacy.
A number of therapies in intermediate and advanced clinical trials hold the promise of adding several additional agents to the growing armamentarium of MS therapeutics. These include monoclonal antibodies that target CD25 (Daclizumab), CD20 (Ocrelizumab, Ofatumumab), or CD52 (Alemtuzumab); the oral therapy laquinimod, a number of antigen-specific therapeutic approaches, and cell-based and CNS-directed therapies (including those targeting immune modulation and/or reparative functions). A growing number of agents are being evaluated in patients with SPMS/PPMS, and there is evolving discussion about approaches to managing therapies (escalation vs. Induction/maintenance); combination approaches (serial or concurrent) and efforts to move towards more personalized therapeutic paradigms. Here we will briefly consider the clinical profiles and presumed therapeutic mode of action (MOA) of selected emerging therapies and consider the approaches that may be used by the clinician to reconcile the growing number of options and increased complexity of management.
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