New therapeutic approaches for a changing MS scenario
GENERAL INFORMATION

VENUE
The Conference will take place at the:

Sheraton Rio Hotel
Avenida Niemeyer 121
Leblon Rio de Janeiro
Rio de Janeiro 22450-220 · Brazil
Phone +55 (21) 2274 1122
http://www.sheraton-rio.com/

LANGUAGE
The official language of this Conference will be English.

TRAVEL INFORMATION
Rio de Janeiro is the capital city of the State of Rio de Janeiro.
The city is famous for its natural settings, its carnival celebrations, samba, Bossa Nova and hotel-lined tourist beaches, such as Copacabana, Ipanema and Leblon. Some of the most famous landmarks in addition to the beaches include the giant statue of Christ, known as Christ the Redeemer, the Sambódromo, a giant permanent parade stand used during Carnival and Maracanã stadium, one of the world’s largest football stadiums. The city is divided into the historic downtown (Centro), the tourist-friendly South Zone, with its world-famous beaches, the residential North Zone and the West Zone. Centro is the historic centre of the city, as well as its financial centre, some of the largest companies in Brazil have their head offices here. Sites of interest include the Paço Imperial built during colonial times, many historic churches such as the Candelária Church, the colonial Cathedral and the modern-style Rio de Janeiro Cathedral, several landmarks of the Belle Époque of Rio such as the Municipal Theatre and the National Library building, and several museums.
Serono Symposia International Foundation

Conference on:

NEW THERAPEUTIC APPROACHES FOR A CHANGING MS SCENARIO

Rio de Janeiro, Brazil - May 21-22, 2010

AIM OF THE CONFERENCE

This Conference is aimed to provide participants with an updated overview of pathogenetic mechanisms, management tools and future therapeutic targets for both multiple sclerosis (MS) and neuromyelitis optica (NMO). Experts from Latin America and Europe will present some of the hottest topics related to these diseases and interactive sessions will offer the opportunity to share their knowledge and experience with participants.

LEARNING OBJECTIVES

Participants in this Conference will:

• Acquire information on MS and NMO pathogenetic mechanisms and pharmacological targets
• Be updated on diagnostic tools aimed to diagnose and monitor MS and NMO
• Improve their knowledge on therapeutic approaches
• Share knowledge and experience with LATAM and international speakers

TARGET AUDIENCE

Clinicians managing patients with MS.

ACCREDITATION

Serono Symposia International Foundation (www.seronosymposia.org) has submitted this program "New therapeutic approaches for a changing MS scenario" (Rio de Janeiro, Brazil - May 21-22, 2010) for accreditation by the European Accreditation Council for Continuing Medical Education (EACCME).

All Serono Symposia International Foundation programs are organized solely to promote the exchange and dissemination of scientific and medical information. No forms of promotional activities are permitted. There may be presentations discussing investigational uses of various products. These views are the responsibility of the named speakers, and do not represent an endorsement or recommendation on the part of Serono Symposia International Foundation. This program is made possible thanks to the unrestricted Educational grant received from: Centre d’Esclerosis Multiple de Catalunya, Vall d’Hebron University Hospital, ComtedMed, Congrex Sweden, Congrex Switzerland, Cryo-Save, Datanalysis, Fundación IVI, ISFP International Society for Fertility Preservation, ISMH International Society of Men’s Health, K.I.T.E., Merck Serono, Meridiano Viaggi e Turismo, Ministry of Health of the State of Israel, University of Catania.
SCIENTIFIC ORGANIZERS

Oscár Fernández
Department of Neurology
Hospital Regional Universitario Carlos Haya
Malaga, Spain

Regina Papais Alvarenga
Universidade Federal do Estado do Rio de Janeiro
Centro de Ciências Biológicas e da Saúde, Neurologia
Rio de Janeiro, Brazil

LIST OF SPEAKERS AND CHAIRMEN

José Carlos Álvarez-Cermeño
Department of Neurology
Ramón y Cajal Hospital
Madrid, Spain

Txomin Arbizu
Multiple Sclerosis Unit
Department of Neurology
Hospital Universitario de Bellvitge
Barcelona, Spain

Raul Arcega
Neurologist Unidad Medica de Alta Especialidad
Centro Medico Nacional Manuel Avilla Camacho
Mexico City, Mexico

Bonaventura Casanova
Department of Neurology
University Hospital La Fe
Valencia, Spain

Giancarlo Comi
Institute of Experimental Neurology
University Vita-Salute IRCCS
San Raffaele Hospital
Milano, Italy

Francisco Coret Ferrer
Department of Neurology
Hospital Clínico Universitario
Valencia, Spain

Jorge Correale
Institute for Neurological Research
Dr. Raúl Carrea, FLENI
Buenos Aires, Argentina

Edgardo Cristiano
Medicine, Instituto Universitario
Hospital Italiano de Buenos Aires
MS Center, Department of Neurology
Hospital Italiano de Buenos Aires
Buenos Aires, Argentina

Carlos Cuevas Garcia
Department of Neurology
Instituto Mexicano del Seguro Social
Mexico City, Mexico

Oscár Fernández
Department of Neurology
Hospital Regional Universitario Carlos Haya
Malaga, Spain

Juan Antonio García Merino
Neuroimmunology Unit
Department of Neurology
Hospital Puerta de Hierro
Universidad Autonoma de Madrid
Madrid, Spain

Marco Lana-Peixoto
CIEM MS Research Center
Federal University of Minas Gerais
Medical School
Belo Horizonte, Brazil

Rafael Lander
Division of Neurology
Centro Médico Docente La Trinidad
Caracas, Venezuela

Miguel Angel Macias
Department of Clinical Neurology
Centro Médico Nacional de Occidente, IMSS
Clinical Research
Mexican Multiple Sclerosis Foundation
Guadalajara, Mexico
Oliver Neuhaus  
Department of Neurology  
Kliniken Landkreis Sigmaringen  
Sigmaringen, Germany

Regina Papais-Alvarenga  
Universidade Federal do Estado do Rio de Janeiro  
Centro de Ciências Biológicas e da Saúde, Neurologia  
Rio de Janeiro, Brazil

Arnoldo Soto  
Department of Neurology  
Hospital Domingo Luciani - IVSS  
Caracas, Venezuela

Antonio Uccelli  
Department of Neurosciences  
Ophthalmology and Genetics  
University of Genoa  
Genoa, Italy

Heinz Wiendl  
Department of Neurology, Inflammatory Diseases  
of the Nervous System and Neurooncology  
Münster, Germany

---

Scientific Secretariat  
Serono Symposia International Foundation  
Salita di San Nicola da Tolentino, 1/b - 00187 Rome, Italy  
Senior Project Manager: Francesca Caputo  
Tel.: +39-06-420 413 568 - Fax: +39-06-420 413 677  
E-mail: info@seronosymposia.org  
Serono Symposia International Foundation  
is a Swiss Foundation with headquarters in  
14, rue du Rhône, 1204 Genève, Switzerland

Organizing Secretariat  
Meridiano Congress International  
Via Mentana, 2/B - 00185 Rome, Italy  
Congress Coordinator: Federica Russetti  
Phone: +39-06-88595 209 - Fax: +39-06-88595 234  
E-mail: f.russetti@meridiano.it
SCIENTIFIC PROGRAM
FRIDAY - MAY 21, 2010

9.00  Serono Symposia International Foundation (SSIF) Opening
      Giancarlo Comi, Italy
      President of SSIF Scientific Committee

9.15  Welcome and introduction
      Regina Papais-Alvarenga, Brazil - Oscár Fernández, Spain

SESSION I

MOLECULAR BASIS TO TARGET MS & NMO

Chairmen: Oscár Fernández, Spain - Rafael Lander, Venezuela

9.30  L1: Immunopathogenesis, neuropathology and clinical facts of MS: an integrated view
      Juan Antonio García Merino, Spain

10.00 L2: The role of T and B lymphocyte in MS pathogenesis
         Heinz Wiendl, Germany

10.30 L3: CSF analysis to identify immunological profile
         José Carlos Álvarez-Cermeño, Spain

11.00 Discussion

11.15 Coffee Break

11.45 L4: MRI and other paraclinical tools to monitor disease evolution
         Bonaventura Casanova, Spain

12.15 L5: Neuromyelitis optica as a separate entity: differential pathogenic and epidemiological aspects
         Marco Lana-Peixoto, Brazil

12.45 L6: Clinical features and therapeutic approaches for neuromyelitis optica
         Regina Papais-Alvarenga, Brazil

13.15 Discussion

13.30 Lunch
SESSION II

OPTIMAL TREATMENT STRATEGIES IN MS

Chairmen: Giancarlo Comi, Italy - Edgardo Cristiano, Argentina

14.30  L7: Immunological basis behind current MS treatments
        Oliver Neuhaus, Germany

15.00  L8: Rational basis for early MS treatment
        Bonaventura Casanova, Spain

15.30  L9: Monitoring treatment response for an optimal therapy
        Miguel Angel Macías, Mexico

16.00  Discussion

16.15  Coffee Break

16.45  L10: Therapeutic strategies: escalating, induction or combination
        Oscár Fernández, Spain

17.15  L11: Spanish Consensus Guidelines for treatment optimization
        Txomin Arbizu, Spain

17.45  L12: Treatment optimization consensus in LATAM
        Arnoldo Soto, Venezuela

18.15  Discussion

18.30  End of the day
SATURDAY - MAY 22, 2010

SESSION III

CHANGING APPROACHES FOR THE FORTHCOMING MS SCENARIO

Chairmen: Francisco Coret Ferrer, Spain - Regina Papais-Alvarenga, Brazil

8.45  L13: New therapeutic targets for future MS agents
      Jorge Correale, Argentina

9.15  L14: New oral therapies in MS and their role in the new treatment strategies
      Giancarlo Comi, Italy

9.45  L15: New injectable therapies in MS: monoclonal antibodies
      Edgardo Cristiano, Argentina

10.15 Discussion

10.30 Coffee Break

11.00 L16: New therapies with bone marrow derived stem cells
         Antonio Uccelli, Italy

11.30 L17: The challenge of stem-cell therapy in MS
         Oscár Fernández, Spain

12.00 Panel on:
      Pathogenesis and Pathophysiology

   Chairmen: Giancarlo Comi, Italy
              Juan Antonio García Merino, Spain

   Panelists: Marco Lana-Peixoto, Brazil
              Regina Papais-Alvarenga, Brazil

12.45 Panel on:
      Treatment algorithms

   Chairmen: Oscar Fernández, Spain
              Regina Papais-Alvarenga, Brazil

   Panelists: Raul Arcega, Mexico
              Jorge Correale, Argentina
              Edgardo Cristiano, Argentina
              Carlos Cuevas García, Mexico
              Oliver Neuhaus, Germany

13.30 Concluding remarks

13.45 End of the Conference and Closing Lunch
DISCLOSURE OF FACULTY RELATIONSHIPS

Serono Symposia International Foundation adheres to guidelines of the European Accreditation Council for Continuing Medical Education (EACCME) and all other professional organizations, as applicable, which state that programs awarding continuing education credits must be balanced, independent, objective, and scientifically rigorous. 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 program (which may reflect clinical experience, the professional literature or other clinical sources known to the presenter). We ask all presenters to provide participants with information about relationships with pharmaceutical or medical equipment companies that may have relevance to their lectures. This policy is not intended to exclude faculty who have relationships with such companies; it is only intended to inform participants of any potential conflicts so participants may form their own judgments, based on full disclosure of the facts. Further, all opinions and recommendations presented during the program and all program-related materials neither imply an endorsement, nor a recommendation, on the part of Serono Symposia International Foundation. All presentations solely represent the independent views of the presenters/authors.

The following faculty provided information regarding significant commercial relationships and/or discussions of investigational or non-EMA/FDA approved (off-label) uses of drugs:

José Carlos Álvarez-Cermeno
Declared receipt of grants and contracts from Merck-Serono, Bayer-Schering, Biogen Idec and to receive honoraria or consultation fees from Merck-Serono, Bayer-Schering, Biogen Idec, Teva, Sanofi Aventis. Declared also to be a member of the following companies advisory board, board of directors or other similar groups: Merck-Serono, Bayer-Schering, Biogen Idec.

Raul Arcega
Declared no potential conflict of interest.

Bonaventura Casanova
Declared to be a member of the following companies advisory board, board of directors or other similar groups: Merck-Serono, TEVA, Sanofi Aventis.

Francisco Coret Ferrer
Declared to be member of TEVA advisory board, board of directors or other similar groups.

Jorge Correale
Declared receipt of grants and contracts from Novartis Clinical Trials and to receive honoraria or consultation fees from Merck-Serono and Biogen Idec, Teva, Sanofi Aventis. Declared also to be a member of the following companies advisory board, board of directors or other similar groups: Merck-Serono, Biogen Idec.

Edgardo Cristiano
Declared no potential conflict of interest.

Carlos Cuevas Garcia
Declared receipt of grants and contracts from Teva, Merck Serono and Biogen and to receive honoraria or consultation fees from Teva and Biogen Idec. Declared also to be a member of Teva advisory board, board of directors or other similar groups.

Oscár Fernández
Declared no potential conflict of interest.

Juan Antonio García Merino
Declared receipt of honoraria or consultation fees from Merck-Serono, Biogen Idec and Novartis.

Rafael Landet
Declared receipt of honoraria or consultation fees from Advisory Board Meetings.

Oliver Neuhaus
Declared no potential conflict of interest.

Regina Papais-Alvarenga
Declared receipt of grants and contracts from Merck-Serono, Teva, Novartis and Biogen Idec and to receive honoraria or consultation fees from Bayer-Schering. Declared also to be a member of Biogen Idec advisory board, board of directors or other similar groups.

Arnoldo Soto
Declared receipt of honoraria or consultation fees from Abbott, Bayer and Merck Serono.

Antonio Uccelli
Declared receipt of grants and contracts from Sanofi Aventis and to receive honoraria or consultation fees from Genetech, Roche, Allergan and Merck-Serono. Declared also to be a member of the following companies advisory board, board of directors or other similar groups: Roche and Allergan.
The following faculty have provided no information regarding significant relationship with commercial supporters and/or discussion of investigational or non-EMEA/FDA approved (off-label) uses of drugs as of April 30, 2010.

Txomin Arbizu
Giancarlo Comi
Marco Lana-Peixoto
Miguel Angel Macias
Heinz Wiendl

All Serono Symposia International Foundation programs are organized solely to promote the exchange and dissemination of scientific and medical information. No forms of promotional activities are permitted. There may be presentations discussing investigational uses of various products. These views are the responsibility of the named speakers, and do not represent an endorsement or recommendation on the part of Serono Symposia International Foundation. This program is made possible thanks to the unrestricted Educational grant received from: Centre d’Esclerosi Múltiple de Catalunya, Vall d’Hebron University Hospital, ComtecMed, Congrex Sweden, Congrex Switzerland, Cryo-Save, Datanalysis, Fundación IVI, ISFP International Society for Fertility Preservation, ISMH International Society of Men’s Health, K.I.T.E., Merck Serono, Meridiano Viaggi e Turismo, Ministry of Health of the State of Israel, University of Catania.
ABSTRACTS (L1 – L17)
The last two decades have witnessed a tremendous advance in the knowledge of almost every aspect of multiple sclerosis (MS). The progress in crucial disciplines such as epidemiology, genetics, molecular biology, immunology, pathology, imaging and therapeutics has disentangled some important questions, while showing, at the same time, the complexity of the disease. One of the most important changes in MS, in our view, has been the recognition of the role of axonal loss as a basic component of the disease, responsible for the irreversible disability. MS is considered a disorder in which immune-mediated, neuroinflammatory phenomena predominate in the first years, with progressive loss of axons being the most prominent aspect in late phases. It is generally accepted that MS is a heterogeneous disorder, in terms of clinical phenotype, outcome and response to medications. In a series of selected samples of MS tissue, four main pathological subtypes of MS, mutually exclusive, have been described according to the immune findings. Whether or not MS represents a single disease or a syndrome resulting from different diseases is a matter of debate with practical consequences for prognosis and therapy. In this presentation the main views on immune pathogenesis, and neuropathology are reviewed with special emphasis on their relevance for the clinical course of MS.
THE ROLE OF T AND B LYMPHOCYTES IN MS PATHOGENESIS

Heinz Wiendl
Department of Neurology, Inflammatory Diseases of the Nervous System and Neurooncology, Münster, Germany

The characterization of pathological and immunological features of MS lesions together with recent functional studies elucidating the interactions of the immune components with central nervous system structures has provided novel insights into the cellular and molecular mechanisms of inflammatory CNS damage. Histopathological classification of MS lesions demonstrated the heterogeneity of MS lesions presenting as four different patterns (patterns I-IV). While cellular and humoral immune components are the prevailing elements characterizing pattern I and II, primary "glial damage" with less inflammation characterizes pattern III and IV lesions. In parallel, last years advanced our knowledge on the mechanisms of CNS immunity and immune surveillance.

The presentation will summarize novel insights in the role of T and B lymphocytes in the pathogenesis of MS. Especially the mechanisms how the immune system interacts with glial cells and neurons, what the damaging effector components may be and what the mechanisms of immune-mediated CNS damage as opposed to protection are. Specific focus will be on CD8 T cell attacking neurons, thus contributing to the neuronal damage envisaged early in MS patients. Apart from the destructive consequences of immune-mediated damage, specific focus will thus be put on the role of immune protective mechanisms within the CNS, that may be derived from CNS parenchymal cells or result from immune cells, especially the subset of regulatory T cells (concept of protective (auto)immunity). Understanding the mechanism of nervous and immune system crosstalk greatly aids at understanding the role of the local CNS environment in its interactions with immune components. These aspects are relevant both from an immune-pathogenetic as well as from a therapeutic view.
CSF ANALYSIS TO IDENTIFY IMMUNOLOGICAL PROFILE

José Carlos Álvarez-Cermeño
Department of Neurology, Ramón y Cajal Hospital, Madrid, Spain

CSF study is an accurate method to demonstrate immunological alterations in neurological patients. The presence of oligoclonal bands of IgG (OCGB) is a hallmark of multiple sclerosis (MS) and an ancillary tool to confirm the diagnosis. It also has a prognostic value in individuals with clinically isolated syndromes. On the other hand, MS patients with oligoclonal bands of IgM against lipids (OCMB) develop an aggressive disease in terms of relapse rate and disability progression. Interestingly, patients with primary-progressive MS OCMB lack. Therefore, different patterns of OCB identify distinct forms of MS evolution. It suggests different pathophysiological mechanisms in the disease, in line with other data previously published.
MRI AND OTHER PARACLINICAL TOOLS TO MONITOR DISEASE EVOLUTION

Bonaventura Casanova
Department of Neurology, University Hospital La Fe, Valencia, Spain

Multiple sclerosis is primarily an inflammatory disorder of the brain and spinal cord in which focal lymphocytic infiltration leads to damage of myelin and axons. Initially, inflammation is transient and remyelination occurs but is not durable. However, over time, the pathological changes become dominated by widespread microglial activation associated with extensive and chronic neurodegeneration, the clinical correlate of which is progressive accumulation of disability.

MRI is integrated in the overall diagnostic scheme of the disease, because of its unique sensitivity to demonstrate the spatial and temporal dissemination of demyelinating plaques in the brain and spinal cord. Conventional MRI techniques (cMRI), such as T2-weighted (T2W) sequences and gadolinium-enhanced T1-weighted sequences, are important tools for diagnosing MS, as well as for understanding the natural history of the disease and monitoring the efficacy of experimental treatments. New MRI techniques (T1- hypo-intense lesions, quantitative analysis of global and regional brain volume, magnetization transfer MR imaging, diffusion-weighted MR imaging, and proton MR spectroscopy) measure the more destructive aspects of MS pathology and monitor the reparative mechanisms. Optical coherence tomography (OCT) is another paraclinical tool for diagnosing and could be a predictive marker of axonal damage.
NEUROMYELITIS OPTICA AS A SEPARATE ENTITY: DIFFERENTIAL PATHOGENIC AND EPIDEMIOLOGICAL ASPECTS

Marco Lana-Peixoto
CIEM MS Research Center, Federal University of Minas Gerais Medical School, Belo Horizonte, Brazil

Abstract not in hand at the time of going to press.
Neuromyelitis optica (NMO) is a rare inflammatory demyelinating immune-mediated central disease characterized mainly by acute index events: optic neuritis (ON) and transverse myelitis (TM). For over a century this rare syndrome was referred as Devic’s disease and diagnosis based on identification of ON and TM occurring simultaneously or within a short time. The relapsing form (RNMO) that matches differential diagnosis with Multiple Sclerosis (MS) was only recognized in the last decade. The report of a serum antibody with high specificity for NMO called anti-AQP4 and the description of symptomatic brainstem (BS) and cerebral lesions in patients with a well-established diagnosis of NMO lead to a revision of the diagnostic criteria. Nowadays the diagnosis is based on acute events of ON and TM, and two of the three laboratory criteria: cranial MRI normal or not suggestive of MS, extensive longitudinal spinal cord lesion and positivity of the anti AQP4. The disease affects mainly non-Caucasians living in Asia or tropical countries.

The natural history of this severe disease will be presented based on a longitudinal study of a large cohort of patients from Rio de Janeiro (Brazil). We will discuss the results of treatment with drugs approved drugs for MS and also with steroids, intravenous immunoglobulin, plasma exchange, immunosuppressive agents and monoclonal antibodies.
Multiple sclerosis (MS) is the commonest inflammatory disorder of the central nervous system, one of the commonest neurological disorders in younger adults and the leading cause of neurological disability in this age group. Throughout the last years, the arsenal of immunomodulatory and immunosuppressive agents approved for the treatment of MS has increased. Furthermore, a large variety of new drugs and compounds are currently being investigated in preclinical and clinical trials. In parallel, new evidence regarding the underlying pathogenesis of the disease as well as mechanisms of action of the different agents has been advanced.

In this lecture, the putative mechanisms of action in vitro and in vivo of current treatments are summarized against the background of current knowledge of the etiology and pathogenesis of MS.
RATIONAL BASIS FOR EARLY MS TREATMENT

Bonaventura Casanova
Department of Neurology, University Hospital La Fe, Valencia, Spain

There are two main pathologic features in MS patients: inflammation with demyelination (mainly related to clinical relapses and MRI T2 lesion load and Gadolinium enhancing lesions) and axonal degeneration (mainly related to clinical disability progression and MRI brain atrophy), although the exact relation between them is not clear yet. However, the number and severity of relapses and the T2 lesion load increase during the first years have shown to be robust predictors of long term disability. Immunomodulatory therapies (IMM) primarily act on the inflammatory part of the disease decreasing relapses and the appearance of new lesions in the MRI, and they have shown to be effective from the first relapse. We would expect that they could prevent at some extent long term disability, although their effect over degeneration parameters has not been clearly established. MS course is very heterogenic, and not every patient will need IMM treatment. We need to select patients for early treatment based on clinical, MRI and CSF biomarkers.
Monitoring MS treatment requires careful consideration of different scenarios. Patients on disease modifying drugs may show stability and no changes to treatment are needed. But when a breakthrough is present we have to establish specific ways of evaluating: (i) suboptimal response, (ii) non compliance, (iii) presence of neutralizing antibodies or (iv) a higher level of disease activity.

Different approaches have been proposed in order to optimize and monitor treatments, including the analog model that analyses relapses, progression and MRI.

It is very important for clinicians to define the precise moment to acknowledge therapeutic failure and to proceed to change doses or treatment. We have to evaluate the impact of neutralizing antibodies and also to monitor the treatment adherence.

The surge of new therapies for MS increases the options for rapidly progressive patients and for those considered as “non responders”. However, we have to be careful to evaluate the risk/benefit balance of present and future therapeutic agents.
Multiple sclerosis (MS) is assumed to be an autoimmune disease for which we have several available therapies. Usually patients present a first clinical episode of demyelination, called clinically isolated syndrome (CIS). In case of risk of conversion to MS they are usually treated with an immunomodulator beta (interferons or glatiramer acetate). After a variable follow up period, normally lasting one year, if there is some persistent activity (exacerbations or active lesions in MRI), patients can be classified either as suboptimal responders or non-responders, based on the amount of activity. In case of treatment failure, the potency of immunosuppression is increased (escalating therapy).

Some cases of MS are particularly severe from disease onset and a different strategy can be used. In this case more powerful drugs are used early (induction therapy) and, once the disease is stable for a given period, patients are down-escalated to a less aggressive treatment with an immunomodulator.

In this presentation I will discuss the evidence, consensuses, advantages and disadvantages of both therapeutic approaches.
SPANISH CONSENSUS GUIDELINES FOR TREATMENT OPTIMIZATION

Txomin Arbizu
Multiple Sclerosis Unit, Department of Neurology, Hospital Universitario de Bellvitge, Barcelona, Spain

Abstract not in hand at the time of going to press.
TREATMENT OPTIMIZATION CONSENSUS IN LATAM

Arnoldo Soto
Department of Neurology, Hospital Domingo Luciani - IVSS, Caracas, Venezuela

Latin America is different from Europe and North America. To address the topic of Multiple Sclerosis (MS) in Latin America is challenging as many obstacles must be overcome such as: MS was considered a rare disease in LATAM, professionals and healthcare organizations were not interested in MS and there is a lack of human, technical and economic resources. The current situation shows a large contrast among LATAM countries, that becomes more obvious when we include the disparity of economic resources available for accessible healthcare and the ethnic heterogeneity in the region. For these reasons it is necessary to consolidate the evidence available for the treatment of MS patients in Latin America in order to create Guidelines or Recommendations for optimizing the treatment of MS in the region. To fulfill the main objective, groups of experts from Argentina, Brazil, Colombia, México and Venezuela elaborated a list of statements related to the use of immunomodulatory agents in the different clinical forms of the disease and the strategies that should be considered in cases of suboptimal response. The conclusions are the following: McDonald’s Criteria were designed to improve the early and precise diagnosis of MS, they are not always applicable in Latin America and they should not be used for decisions on disease modifying drug (DMD) related treatments. Regarding CIS, there is a high risk of evolution to CDMS if MRI lesions suggestive of MS and multiregional symptoms are present, even if OCB in the CSF and abnormal VEP response are present. There is enough evidence for the use of DMDs to delay the conversion to CDMS with the use of IFNβ-1a (low dose), IFNβ-1b and glatiramer acetate. Evidence is available that supports the use of DMDs in RRMS and SPMS with relapses or MRI activity. They modify the natural history of the disease, but they do not cure and no evidence is available for the use of DMDs in PPMS. Availability of DMDs in adults is not limited by age, EDSS, number of relapses or MRI findings. Inflammation and axonal damage occur early in the disease so early use of DMDs is recommended. There is variability of an inter-Individual response to DMDs. Non-responders should be identified by considering the number of relapses, progression and MRI findings. To switch to other therapies, if necessary, is an option, according to individual needs, but a treatment must be maintained for at least 6 months before considering switching. Some evidence suggests that high-dose interferon could be superior to low dose in RRMS. A good responder to DMDs should be maintained in the same treatment, and reduction of dose is not recommended in these patients. The role of NABs is not clear and persistent high titers of NABs could be associated with loss of efficacy, but changes in treatments must be based on clinical response. Most patients receiving DMDs, present side effects that disappear in weeks or months. When they persist, change of treatment must be considered. Immunosuppressive therapy must be considered in non responders to DMDs, especially in patients with rapid EDSS progression. The drug recommended is mitoxantrone at the total dose of 100–120 mg. Some considerations exist concerning cardiotoxicity and other side effects, such as leukemia and other neoplasm. Considering availability of these drugs, access to all DMDs for patients with MS must be assured.
NEW THERAPEUTIC TARGETS FOR FUTURE MS AGENTS

Jorge Correale
Institute for Neurological Research Dr. Raúl Carrea, FLENI, Buenos Aires, Argentina

Therapeutic options for multiple sclerosis (MS) are rapidly expanding. What was once considered a disease with little hope for treatment has now become the target of extensive drug development. Current therapies have demonstrated efficacy in limiting disease impact, but treatment that is fully effective in all patients has yet to be found, making evident the need for newer and better therapies with less serious side effects.

A first group of new drugs targeting specific steps in the development of inflammatory processes present in MS includes DNA vaccines, altered peptide ligands (APL) and soluble peptides, seeking to inducing self-tolerance in autoimmune diseases. DNA vaccination has shown promising results in EAE models and in preliminary clinical trials in MS, as an antigen-specific strategy. Results from ongoing studies are warranted to confirm its efficacy and safety. In contrast, results from initial APL trials have dampened enthusiasm for this strategy. However, perhaps lower dose APL studies will provide more favorable clinical results. The use of soluble peptides is highly dependent on identifying specific antigen targets participating in the MS-related immune response. While early trials have been well tolerated, little evidence exists to suggest that targeting a single epitope has much impact on the course of the disease.

Other possible approaches are directed to target specific co-stimulatory pathway components such as CD40/CD40L, B7, CD28 and CTLA4. Although co-stimulatory blockade does have certain intrinsic advantages (self-antigens in MS need not be identified), it remains to be seen whether it will have an effect on T cells already been primed by autoantigens.

Nuclear hormone receptors are a large class of intracellular ligand-activated transcription factors. Agonists for some receptors, such as the peroxisome proliferator-activated receptor (PPAR) have caused significant improvement of clinical EAE, making them an attractive alternative for MS treatment. Clinical trials with PPAR-γ agonists are currently under way and results eagerly anticipated.

Several transcription factors are critical in determining naïve T cell differentiation, and inhibition of some of these transcription factors such as T-bet through small interfering RNA (si-RNA) has been shown to suppress IFN-γ and STAT-1 production. Transcription factor manipulation may offer a great deal of insight into molecular regulation of the immune response. Although these strategies are clearly in infancy stages in terms of their application in humans.

A second group of new strategies in MS is directed at promoting neuroprotection, through preventing axonal damage, and inducing remyelination. Promising experimental studies and early results using different agents, such as immunophilins, AMPA/glutamate receptors, and erythropoietin, have been reported in preliminary trials, nevertheless, a lot of emphasis continues to be placed on neurotrophic and growth factors, based on the pathophysiology of the disease. Several growth factors have been proposed as preserving axons and inducing remyelination by acting directly on neurons and their processes or on oligodendrocytes. However, an effective treatment will probably require the combination of several molecules, administered at different time points during disease development.

Another way to promote the axonal growth and induce remyelination is by blocking the inhibitors of neurite outgrowth released after CNS injuries and demyelination. Blocking molecules, such as NOGO o Lingo using either specific monoclonal antibodies or vaccination has been beneficial in spinal cord injuries, and may prove useful in MS as well. Another way to counteract axonal growth inhibition triggered by NOGO receptor activation is to interfere with the signaling pathway, blocking GTPase Rho or increasing intracellular AMP.
NEW ORAL THERAPIES IN MS AND THEIR ROLE IN THE NEW TREATMENT STRATEGIES

Giancarlo Comi
Institute of Experimental Neurology, University Vita-Salute IRCCS, San Raffaele Hospital, Milano, Italy

Actually approved disease modifying drugs (DMDs) for relapsing-remitting multiple sclerosis include recombinant interferon (IFN-beta) and glatiramer acetate (GA). All these immunomodulatory treatments have been shown to reduce the frequency and severity of relapses, as well as reducing progression of neurological disability. However all DMDs are administered parenterally and need frequent injections which may be inconvenient and uncomfortable for patients. In addition, not all patients respond adequately and common side effects associated with these therapies may reduce adherence. The development of drugs with easier administration, such as oral agents, would further promote adherence, increase patient satisfaction and thereby improve efficacy. Two phase III clinical trials CLARITY and TRANSFORM have provided promising results for cladribine and fingolimod respectively.

The results of the CLARITY study show that annual short-course treatment with both doses (3.5 mg/kg and 5.25 mg/kg) of cladribine tablets led to a significant reduction in the rate of clinical relapses, disability progression and brain lesions, as well as a significant increase in the proportion of patients who remained relapse-free. Overall, the frequencies of adverse events in both cladribine treatment groups were comparable to those observed in the placebo group dose.

The results of TRANSFORM study, also show a significant reduction in annualized relapses rate and MRI activity. During this study, two fatal viral infections occurred. Moreover, the FREEDOMS study demonstrated a significant reduction of disease activity of both doses of fingolimod against interferon beta 1a i.m.. The safety profile of the drug open some concern for the risk herpes infections and cardiovascular problems.

Other oral drugs in earlier phase of the development include BG12, teriflunomide and laquinimod For all these three drugs, a preliminary efficacy emerged from Phase II studies and phase III studies are ongoing.
NEW INJECTABLE THERAPIES IN MS: MONOCLONAL ANTIBODIES

Edgardo Cristiano
Medicine, Instituto Universitario, Hospital Italiano de Buenos Aires, MS Center, Department of Neurology, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina

Whereas current immunomodulatory agents have demonstrated beneficial effects on the disease course, more effective drugs are needed. In the last decade, emerging therapies like oral immunomodulatory / immunosuppressive drugs and monoclonal antibodies (mAb) demonstrated higher efficacy in limiting the impact of the disease. Monoclonal antibodies are injectable proteins that target specific molecules involved in different steps of the pathophysiological cascade of MS promising a more specific and rational approach. Currently, natalizumab is the only approved mAb for relapsing MS, however there are at least three other molecules (rituximab, alemtuzumab and daclizumab) in advanced phases of clinical research. Moreover, these agents are under investigation for progressive forms of the disease. The scope of this lecture is to review the clinical results of these new drugs and their benefit/risk profiles in a new therapeutic scenario.
NEW THERAPIES WITH BONE MARROW DERIVED STEM CELLS

Antonio Uccelli
Department of Neurosciences Ophthalmology and Genetics, University of Genoa, Genoa, Italy

The recent advances in our understanding of stem cell biology, the availability of innovative techniques, which allow obtaining large scale of stem cells, and the increasing pressure from the multiple sclerosis (MS) patients community, seeking for tissue repair strategies, have launched stem cells treatments as one of the most exciting and difficult challenge in the MS field. I will provide an overview about the current status of stem cells research in MS focusing on secured actuality, reasonable hopes and unrealistic myths.

Results obtained from small clinical studies with transplantation of autologous hematopoietic stem cells have demonstrated that this procedure is feasible and possibly effective in severe forms of MS, but tackles exclusively inflammation without affecting tissue regeneration. Results from preclinical studies with other adult stem cells, such as bone marrow derived mesenchymal stem cells, have shown that they may be a powerful tool to regulate pathogenic immune response and foster tissue repair through bystander mechanisms with limited cell replacement. However, the clinical translation of these results still requires careful evaluation.

Therefore, current experimental evidence suggest that the sound clinical exploitation of stem cells for MS may lead to novel strategies aimed at blocking uncontrolled inflammation, protecting neurons, promoting remyelination but not at restoring the chronically deranged neural network responsible for irreversible disability typical of the late phase of MS.
THE CHALLENGE OF STEM-CELL THERAPY IN MS

Oscar Fernández
Department of Neurology, Hospital Regional Universitario Carlos Haya, Malaga, Spain

Multiple sclerosis (MS) is conceptualized as an autoimmune disease in which we can differentiate two phases during the evolution. In the initial phase there is an intense inflammatory activity mediated by the adaptive immune system. Neuropathologically there is inflammation, demyelination and neuronal degeneration (axonal and neuronal destruction). The clinical counterpart is the presence of exacerbations, with or without accumulation of disability. In this phase the possibility of myelin reparation is high, mediated by oligodendrocyte precursors (OPCs).

After some years of evolution, there is a progressive accumulation of disability independent of exacerbations. In this later phase the innate immune system is more active, and there are inflammatory microglial nodules distributed diffusely throughout the central nervous system. There is a slow destruction of neural structures, axons and neurons, which is accompanied by atrophy detectable in vivo by magnetic resonance imaging and spectroscopy. There is a small capability of remyelination due to several facts: Presence of molecules that inhibit the OPCs migration to the injured areas, reduced number of OPCs, and finally the presence of gliotic scars which difficult the migration of these cells.

The strategies for neural repair would be the blocking of the inhibitory molecules (still in an early research phase) or the increase in the precursor cells. According to animal studies, stem cell therapy probably could replace these cells and be an option for this kind of therapy.

I will present some fundamentals of this therapeutic approach and some protocols of the efforts being performed at the moment in this field.