From bench to bedside: news and views in multiple sclerosis
29 October 2016 - Muscat, Oman
From bench to bedside: news and views in multiple sclerosis

Overview
The multiple sclerosis landscape has changed dramatically in the last few years. New insights into the immunopathogenesis of the disease and the consequent development of new therapeutic approaches, demand continuous medical education in this field. This workshop aims to update and share knowledge about diagnosis and treatment of MS, focusing on a risk benefit profile of available MS drugs and appropriate management of side effects.

Learning objectives
By attending this workshop, participants will be able to:
• Illustrate MS diagnostic criteria and the key elements of differential diagnosis
• Explain the main immunological targets of currently used and future MS treatments
• Describe the risk/safety profiles and appropriate monitoring of MS treatments

Target audience
Neurologists involved in the management of MS patients.

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This live educational workshop is endorsed by MENACtrims  
(Middle East North Africa Committee for Treatment and Research in Multiple Sclerosis).
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This live educational workshop takes place at:

**Intercontinental Muscat**
Al Kharjiya Street
Al Shati Area
Muscat 114, Oman
http://bit.ly/1sg2XYP

**Language**
The official language of this live educational workshop is English.

**CME Provider**
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Programme
Saturday, 29 October 2016

8.45  Welcome and introduction  
A. Al-Asmi (Oman) - G. Comi (Italy) - B. Yamout (Lebanon)

9.00  KNS: Is the epidemiology of MS changing?  
A Focus on Middle East  
B. Yamout (Lebanon)

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<th>Session I</th>
<th>Understanding multiple sclerosis: what have we learned from basic research?</th>
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| 9.20 L1   | Emerging concepts in the pathology of MS  
W. Brück (Germany) |
| 10.05 L2  | Key players in the immunopathogenesis of MS: the synergic role of B and T lymphocytes in disease development and sustainment  
B. Hemmer (Germany) |
| 10.50     | Coffee break |
| 11.20 L3  | Immunomodulation of T and B cells: overview of the mechanisms of action of old and novel molecules to treat MS  
G. Comi (Italy) |
| 12.05 L4  | Old clinical trials for old drugs, new clinical trials for new drugs: what’s changed?  
C. Gasperini (Italy) |
| 12.45     | Lunch |

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<th>Session II</th>
<th>Diagnosing and managing multiple sclerosis: guidance for clinical practice</th>
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| 13.45 E1   | • Diagnostic criteria, phenotypic classification and differential diagnosis  
• Clinical case discussion on differential diagnosis/diagnostic issues  
G. Comi (Italy) |
| 14.30 E2   | • Is the course of MS predictable? The role of imaging and molecular biomarkers from RIS to progressive MS  
• Clinical case discussion on disease staging issues  
N. De Stefano (Italy) |
| 15.15 E3   | • Paediatric MS: differential diagnosis and prognostic factors  
• Clinical case discussion on regional differential diagnosis and individual prognosis  
R.A. Alroughani (Kuwait) |
| 16.00      | Coffee break |
| 16.30 E4   | • Definition of suboptimal response in the new era of MS treatments: MS relapses and disability progression  
• Clinical cases on poor response to treatment  
B. Yamout (Lebanon) |
| 17.15 E5   | • When to switch: navigating treatment algorithms  
• Clinical case discussion on escalation therapy  
C. Gasperini (Italy) |
| 18.00      | Wrap-up discussion and concluding remarks  
End of the workshop |

Legend:  
L: Lecture  
KNS: Keynote speech  
E: Exchange (20’ lecture - 25’ case discussion)
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Declared to be part of a Novartis advisory board, board of directors or other similar group.

Raed A. Alroughani  
Declared no potential conflict of interests.

Wolfgang Brück  
Declared the receipt of grants and contracts from: Teva Pharma, Biogen, Novartis, Genzyme. He declared the receipt of honoraria and consultation fees from: Teva Pharma, Biogen, Merck Serono, Bayer, Novartis, Genzyme advisory board, board of directors or other similar groups.

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Abstracts
The epidemiologic, clinical, radiological, and laboratory characterization of multiple sclerosis (MS) is well documented in Caucasian populations, but data about MS is still limited in the Arab world. A review of all published MS epidemiologic studies from the region shows that most Arab countries fall in the moderate MS prevalence zone, with prevalence rates slightly lower than Southern European but much higher than sub-Saharan African countries. They also demonstrate a clear trend towards increased MS prevalence over the last few decades. The average prevalence of MS in the Middle East is currently around 50 per 100,000. This trend is actually a worldwide phenomenon with recent reports from the MSIF showing that the Global Median Prevalence of MS increased by 10% in 5 years. It is of note that this rise is gender specific and seen mostly in females and leading to a significant in the Female:Male ratio.

This worldwide rise in MS prevalence is probably multifactorial. Longer survival and better/earlier diagnosis due to improved imaging and more sensitive diagnostic criteria are probably contributing to this phenomenon. On the other hand, urbanization, decreased sun exposure, smoking, high BMI (and diet), high salt intake, increased physical and emotional stress, and improved hygiene might all be contributing to an actual increase in the incidence of MS. This rapidly rising prevalence of MS in the Middle East has created major challenges to regional healthcare systems especially with the current political and economic instability in the Middle East. There is an urgent need for medical community education, improved public awareness and patient education, specialized multidisciplinary MS centers, improving research commitment and infrastructure, education of regulatory authorities.
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 in the white and grey matter. 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 demyelinated white matter lesion shows pathological differences between relapsing-remitting and progressive disease stages related to inflammation, axonal degeneration and myelin repair. In the cortical grey matter, three different lesion types are defined with subpial demyelination being the most frequent lesion type. Pathological changes occur also in the normal appearing white and grey matter including microglial activation as well as neuroaxonal damage.

The presentation discusses the pathological events occurring in the above mentioned three compartments including:
1) White matter lesion type (inflammation, axonal pathology, remyelination) in early relapsing-remitting versus progressive MS
2) Gray matter involvement (lesion types, neuronal pathology, meningeal inflammation)
3) Normal appearing brain tissue involvement (microglia activation, axonal and neuronal changes)

The major pathological differences between relapsing-remitting and progressive multiple sclerosis are described also pointing towards new therapeutic targets. In recent years, new entities of inflammatory demyelinating diseases have been identified including neuromyelitis optica and anti-MOG antibody associated demyelination. These entities and differential diagnoses will be demonstrated in detail.
L2. Key players in the immunopathogenesis of MS: the synergic role of B and T lymphocytes in disease development and sustainment

Bernhard Hemmer
Neurology Clinic, University of Munchen, Munchen, Germany

The immune system plays a central role in the pathogenesis of MS. The presence of lymphocytes and macrophages in MS lesions and the association of MS with HLA alleles and many genetic variants tagging particular immune genes define the adaptive immune system, which consists of T- and B-cells, as a key player in the pathogenesis of disease. Inflammation in MS only affects the CNS. Lymphocytes in the CNS of MS patients show evidence of clonotypic accumulation indicating that single T- and B-cells, which underwent extensive clonal expansion in the peripheral immune compartment, selectively enrich in the CNS. This suggests that the CNS in MS is particular prone to inflammation and T- and B-cell are selectively attracted by specific target antigens that are only expressed in the CNS or undergo unique modifications in the CNS. While a CNS infection would be compatible with such a condition, the unsuccessful search for an infectious agent in MS lesions, despite outstanding technological advances in virology and microbiology, supports the concept that the immune response in MS targets CNS autoantigens. Unfortunately the search for the targets of the immune response in MS has remained yet ineffective, although several candidate antigens have been proposed but none yet confirmed.

Why immune responses are initiated against CNS antigens and maintained in MS is unclear. Generation of specific T-cell and B-cell responses, which involves the expansion of large numbers of antigen specific lymphocytes from few precursor cells in the lymph node, requires professional antigen presenting cells (APCs) such as dendritic cells. It is well established that autoreactive lymphocytes, which harbour the potential to induce CNS autoimmunity, are part of the normal lymphocyte repertoire. Two scenarios could be envisioned how pathogenic immune responses to CNS autoantigens might be initiated. The CNS intrinsic model hypothesises that the initial event takes place in the CNS, which leads to the release of CNS antigens to the periphery (either by drainage to the lymph nodes or active carriage by APCs). In the context of a proinflammatory environment, an autoimmune response is generated, which eventually targets the CNS. This scenario is supported by the observation that oligodendrocyte damage may precede immune infiltration in some early MS lesions and oligodendrocyte death may result in immune mediated CNS demyelination in certain experimental animal models. By contrast, the CNS extrinsic model hypothesizes that the initial event takes place outside of the CNS (e.g. in the context of a systemic infection) and leads to an aberrant immune response against the CNS. Several mechanisms such as molecular mimicry (crossreactivity between microbial antigens and autoantigens), bystander activation (priming of autoreactive T cells in the context of other lymphocyte responses) and break of tolerance (priming autoimmune responses by a strong inflammatory stimulus) may account for the initiation of autoimmune responses. The scenario is well represented in the experimental autoimmune encephalomyelitis model, in which an autoimmune response against the CNS is either induced by immunisation with myelin antigens and adjuvants or occurs spontaneously in genetically engineered mice, in which rodent or human myelin antigen specific T- and B-cell receptors are expressed on the majority of circulating lymphocytes. Both scenarios will flow into a detrimental circle of events: tissue damage leads to release of antigens to the periphery, which primes new immune responses in the lymphoid tissue followed by the invasion of lymphocytes into the CNS leading to recruitment of macrophages, which execute tissue damage. The sequence is quite compatible with the relapsing-remitting nature of diseases. Since the process is not self-limiting it is likely that immune regulatory mechanisms fail in MS.

During the progressive phase of disease the contribution of the peripheral immune system decreases and immune responses seem to be confined to the CNS compartment. This view is supported by the observation that systemic immune therapies have no or only minor effects in progressive MS. CNS pathology changes from focal to diffuse white matter injury associated with microglia activation and diffuse lympho- and monocytic infiltrates and increasing cortical involvement, which seems to be associated with lymphoid like follicles in the meninges. This implies that the immune response is sequestered to the CNS compartment with little contribution from the periphery. It is however unclear, whether diffuse tissue injury observed in progressive MS is caused by the compartmentalized immune response or a consequence of diffuse tissue injury caused by other mechanisms. Likewise more axonal injury is observed in demyelinated lesion areas and remyelination seems to protect from axonal damage. Moreover damage or dysfunction of other glia cells may result in secondary neurodegeneration. Thus the ongoing tissue injury in progressive MS might be the consequence of earlier immune mediated damage to glia structures that per se is sufficient to induce secondary neurodegeneration even in the absence of additional inflammatory damage.

Taken together the peripheral immune system plays a central role during the relapsing-remitting phase of disease. In the progressive phase injury seems to arise from a compartmentalized immune response in the CNS, immune independent mechanisms of secondary degeneration as a consequence of earlier immune mediated damage or the combination of both mechanisms.
In recent clinical trials a particular attention should be taken in the interpretation of results since a change in the recruitment of multiple sclerosis patients has occurred in the last 10 years. For several reasons, patients with more benign disease are recently being recruited into clinical trials.

One possible reason is that the modern high resolution MRI allows earlier confirmation of the diagnosis, including subjects with milder symptoms. Moreover, in the old clinical trials, emphasis was placed on clinical activity. In particular history of objective confirmation of 2 relapses in the previous two years was requested. Often the relapses consisted of corticospinal, cerebellar, or brainstem systems which are associated with a poorer prognosis.

Another possible reason for the shift toward more benign subjects in present-day clinical trials is that patients with more aggressive disease may be less likely to be recruited into a trial where there is a chance they may receive a placebo or experimental treatment with an unknown efficacy. This shift toward enrollment of subjects with more benign MS is illustrated by comparisons of the placebo groups from different trials of RRMS. For example the annualized relapse rate of 0.73 for the AFFIRM placebo group was lower than the placebo groups of all 4 other pivotal trials, which ranged from 0.84 to 1.28.

In addition, subjects recruited into present-day clinical trials are enrolled using a different set of diagnostic criteria in the setting of ever-improving diagnostic imaging techniques. The AFFIRM trial enrolled subjects diagnosed using the McDonald criteria, as opposed to the Poser criteria that had been used in prior pivotal trials.

Moreover, the demographics and geographical distribution of MS have changed over time. This change may reflect increasing genetic diversity within the MS population. Subjects from the pivotal trials of IFN-B 1a IM, IFN-B 1b SC, and GA were predominantly recruited from the United States and Canada, The AFFIRM and SENTINEL trials included subjects from a larger number of clinical centers representing greater geographic diversity, enrolling subjects from Europe, North America, Australia, and New Zealand.

In conclusion all these reasons suggest the general MS population is changing over time, making cross-trial comparisons difficult and imprecise especially when comparing trials that were completed more than a decade apart and in different locations.
Several modern MR techniques have been developed and applied during the last couple of decades, providing a number of imaging biomarkers that, complemented with conventional MRI measures, are able to better capture the complexity of the pathological process occurring in the brain of patients with multiple sclerosis (MS). The use of MRI techniques has provided specific information on the heterogeneous pathologic substrate of multiple sclerosis, offering the ability to observe and quantify the evolution of lesions and normal-appearing brain tissue since the pre-symptomatic stage of the disease (i.e., RIS). Moreover, they have emphasized the importance of neurodegeneration in multiple sclerosis and how this can have an impact on physical and cognitive disability. In this respect, advanced neuroimaging techniques such as Magnetization Transfer and Diffusion Tensor as well as molecular imaging techniques have been particularly illuminating. Against this background, the major contributions of quantitative neuroimaging techniques into the understanding of the disease progression and their ability to prognosticate disease evolution will be discussed.
Pediatric-onset MS prevalence and incidence rates are increasing globally. The revised International Pediatric MS group diagnostic criteria improved the accuracy of diagnosis though certain red flags and mimickers (e.g. acute disseminated encephalomyelitis and neuromyelitis optica) should be excluded before establishing definitive diagnosis. Possible etiologic and pathogenic mechanisms were highlighted including both environmental and genetic risk factors. Pediatric MS patients tend to have active inflammatory disease with tendency to have brainstem/cerebellar presentations at onset. Due to efficient repair mechanisms at early life, pediatric MS patients tend to have longer time to reach EDSS 6. Although no therapeutic randomized clinical trials were conducted in pediatric cohorts, open-label multi-center studies reported similar efficacy and safety results with beta interferons, glatiramer acetate and natalizumab to adult cohorts. Several randomized clinical trials assessing the efficacy and safety of oral disease modifying therapies are ongoing in pediatric MS patients.
The aim of treatment in MS is to decrease relapses, MRI activity and disability progression. Pathological studies have shown that axonal loss occurs mostly during the early stages of MS correlating with active inflammation. With the recent advent of highly effective MS therapies, early recognition of suboptimal response to first line disease modifying therapies is crucial in preventing further axonal loss and ultimately accumulation of disability. In the absence of a clear biomarker to predict suboptimal response, clinical and radiological disease activity are commonly used alone or in combination to identify sub responders at risk for poor long term outcomes. Relapses, and new/enhancing lesions on MRI have been shown to predict poor long term outcome in MS patients on treatment. The combination however of both radiological and clinical parameters significantly improves early detection of non responders. Brain atrophy has recently been shown to improve risk assessment when combined with lesion count, but accessibility, reproducibility and other technical issues still limit its use in routine clinical practice.

Many guidelines were developed to predict suboptimal response to therapy in MS, including the Rio score, the Canadian MS Working Group Recommendations, and the MENACTRIMS Guidelines. All of those guidelines used clinical and radiological disease activity, alone or in combination, during the first year of therapy to identify early non responders at risk of future disability accumulation. In the future, the ultimate goal is to develop biomarkers that can clearly predict the response of a single patient to different therapies, and therefore assign each patient to the most appropriate treatment.
In the last 15 years almost 10 effective DMTs are available in the treatment of MS. These drugs differ in their mode of action, route of administration, side effects and risk-benefit profile and becomes challenging to select the appropriate therapy for the individual patient.

The standard treatment strategy followed is the strategy of escalation therapy whereby patients are started with a safe but moderately effective first-line DMT (e.g., IFN-β, GA, teriflunomide) that is advanced to another more potent but more risky second-line and third-line DMT (e.g., fingolimod, natalizumab) in the case of treatment failure or breakthrough disease, which is expected to occur in most patients overtime.

An alternative approach, which is gaining wider support, is the induction therapy strategy involving the short-term use of a potent immunosuppressive therapy (e.g., mitoxantrone, natalizumab, alemtuzumab) followed by long-term maintenance therapy with an immunomodulatory drug.

In this context an important challenge is to choose an alternative therapy in case of treatment failure.

The question is: it is correct to switch from one first-line drug to another first-line drug with different mechanism of action or is more appropriate to switch from a drug of first line to a second-line drug?

We will discuss about these different opportunities in the context of our clinical experience.
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