THE 5TH JOINT TRIENNIAL CONGRESS OF THE EUROPEAN AND AMERICAN COMMITTEES FOR TREATMENT AND RESEARCH IN MULTIPLE SCLEROSIS (AMSTERDAM, NETHERLANDS)
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The 5th Joint Triennial Congress of the European and American Committees for Treatment and Research in Multiple Sclerosis was held from 19-22 of October 2011 in the beautiful city of Amsterdam, Netherlands, a place known in the world for its historic Canal District, world-famous museums, and picturesque scenery. This meeting was hosted by the Amsterdam RAI Congress and Conference Centre wherein more than 7000 participants from all over the world gathered to discuss the latest updates on different aspects of Multiple Sclerosis (MS). More than 15,000 abstracts were accepted. Statistically, it can be considered one of the largest single-gatherings of MS clinicians, researchers, young investigators and also patients suffering from the disorder in the year 2011. In addition, pharmaceutical industries participated in the exhibition hall by presenting a variety of products and services that are vital to medical practitioners, researchers, and scientists who united in this event with a common goal to provide supreme benefits to the people affected by MS, and above all, to completely combat the disease. Aside from the remarkable presentations and posters on advances in all fields of MS, and the large number of abstracts submitted in this meeting, outnumbering those of the previous years, a major breakthrough in this event was the approval of the first oral medication for MS. In relevance to local practice, below is an overview of some interesting abstracts presented at the 5th Joint Triennial Congress of the European and American Committees for Treatment and Research in Multiple Sclerosis.

In conclusion, ECTRIMS 2011 was the largest ever meeting for MS with major breakthroughs, particularly to presentations on oral disease modifying agents, symptomatic treatments, survival, and developments of biomarkers to determine prognosis.

Abstracts

Botulinum toxin type A for the treatment of disabling tremor in multiple sclerosis: a double-blind, randomized controlled study

Background: Upper limb tremor in MS patients is common and disabling. Action tremor, in the form of postural (whilst maintaining a position against gravity), and intention tremor (during movement towards a target), is the most frequent. Medical treatment of MS tremor is unrewarding and surgical intervention is invasive with variable results. In this study the efficacy and side effects of Botulinum Toxin Type A (Botox) was examined in the treatment of MS tremor. Conclusions: This phase II study provides Class I evidence that targeted Botox injections significantly improve upper limb tremor in MS patients.

7T MRI distinguishes Susac syndrome from multiple sclerosis

Introduction: First described in the ‘70s, Susac syndrome consists of the clinical triad of visual disturbances due to branch retinal artery occlusions, sensorineural hearing loss, and encephalopathy. It is considered to be an autoimmune mediated microangiopathy, which consequently leads to microinfarctions and vascular occlusions.
Although an orphan disease, Susac syndrome has yet to be considered in the differential diagnosis in numerous conditions. In particular, the differentiation from multiple sclerosis (MS) can be challenging, since its clinical presentation and paraclinical findings including routine MRI findings partially overlap. Today, ultra high field MRI at 7T depicts white matter lesions with great anatomical details. Here, we studied the potential benefit of 7T MRI in differentiating Susac syndrome from MS. Conclusion: At 7T MRI, lesions in MS patients and patients with Susac syndrome differed with respect to morphology and structural organization. Thus, lesion morphology at 7T may serve as a marker to distinguish Susac syndrome from MS and might be of clinical and therapeutic relevance. In order to confirm our preliminary results further studies including more patients with Susac syndrome are needed.

Effect of fingolimod (FTY720) on disability progression: Application of a transition model to EDSS data collected in the FREEDOMS and TRANSFORMS trials
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Background: The treatment effect of fingolimod on disability progression (DP) in the phase 3 studies FREEDOMS (fingolimod [0.5 or 1.25 mg, once daily] versus placebo [PBO]) and TRANSFORMS (fingolimod [0.5 or 1.25 mg] versus interferon [IFN] beta-1a, intramuscular, every week), in relapsing-remitting multiple sclerosis (RRMS) was assessed on the expanded disability status scale (EDSS). The primary analysis used time to first event as the outcome and utilized survival analysis methods. However, this methodology has some limitations including inefficient use of observed EDSS scores due to censoring. Hence, we applied a new approach to further analyze data. Objectives: To develop a model for assessing fingolimod effects on the probability of transitioning from one EDSS level to another, while correcting for the confounding effect of disease severity and other features observed at baseline (BL). Conclusions: The model successfully characterized DP, as measured by EDSS, in RRMS treated with placebo, IFN beta-1a or fingolimod. The good fit of the model enabled prediction of disability (adjusting for disease severity at BL) in patients treated with fingolimod.

A controlled study on the effect of fingolimod (FTY720) on the immune response following seasonal influenza vaccination and tetanus toxoid booster injection in patients with multiple sclerosis
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Background: Fingolimod (FTY720) 0.5 mg once-daily is the first oral therapy approved in the European Union for relapsing-remitting multiple sclerosis (RRMS) with high disease activity. Fingolimod selectively retains circulating naive and central memory T cells in lymph nodes (LN), sparing effect or memory T cells and reduces peripheral lymphocyte counts by 60-80%. Previous studies suggested that fingolimod may inhibit antibody (Ab) responses to localized antigens (Ag) which require T-/B-cell trafficking to the local Ag-draining LN. Objectives: To evaluate the primary and memory immune response in fingolimod treated MS patients versus placebo by assessing the response against a novel (seasonal influenza vaccine) and a recall antigen (Tetanus Toxoid). Conclusion: Results of this study will provide informative data about fingolimod effects on primary and secondary immune response.

Assessment of anti-JC virus antibodies and JCV DNA in natalizumab treated patients
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Background: Progressive multifocal leukoencephalopathy (PML) is a rare disease caused by the JC virus (JCV), a common polyomavirus. Multiple sclerosis (MS) patients treated with natalizumab have a higher risk of developing...
PML. An enzyme-linked immunosorbent assay (ELISA) to detect JCV specific antibodies in MS patients was developed for identifying patients at higher or lower risk (namely, risk stratification) of developing PML. **Objective:** To assess JCV-specific antibodies in natalizumab treated MS patients and to verify its concordance with blood and urine PCR JCV DNA detection. **Conclusions:** This 2-step assay provides a means to classify MS patients as having detectable or not detectable levels of anti-JCV antibodies, meaning that the subjects have encountered the virus at some point in their lifespan. Prevalence of JCV antibodies positivity in our southern Italy population is comparable with other populations described in the literature. Natalizumab administrations number is not related to the presence of antibodies to the ELISA test, while older age is related to an active proliferation of the virus in the kidneys, that happens in more than a half of antibody positive natalizumab treated patients.

**CSF and serum levels of CXCL13 in MS and NMO**


**Background/goals:** CXCL13, a chemokine that is critical to the formation of germinal centers in lymphoid tissues and is chemotactic for B cells, is implicated in the pathogenesis of multiple sclerosis (MS). Levels of CXCL13 in cerebrospinal fluid (CSF) of MS patients are reported to be higher than in non-inflammatory controls (NIC). The CXCL13 levels may have prognostic significance in MS, and B cell depletion can decrease CXCL13 levels in CSF of patients. The CXCL13 levels in neuromyelitis optica (NMO) have not been reported. We postulate that NMO patients have altered CXCL13 levels, as B lymphocytes appear to be involved in the pathogenesis of NMO given the presence of aquaporin-4 autoantibodies and possible effectiveness of rituximab in the treatment of NMO, which depletes B cells. **Conclusions:** The data presented supports reports of higher levels of CSF CXCL13 in MS compared to NIC. We also demonstrate for the first time, to our knowledge, elevated levels of CSF CXCL13 in NMO. The CSF CXCL13 levels in NMO were highly variable, and were sometimes as high as in patients with CNS lymphoma or viral meningitis. The CSF MBP levels were higher in NMO than MS, perhaps due to its more destructive pathology. In comparison to MS, patients with NMO had elevated CXCL13 levels in serum, likely reflecting the more systemic nature of NMO as compared to MS.

**The effect of laquinimod on immune cell compartment in rodents**

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**Introduction:** Laquinimod is a novel, orally active small molecule that significantly reduced gadolinium enhancing MRI lesions in patients with relapsing remitting multiple sclerosis (RRMS), and is now in phase III clinical trials. Laquinimod has shown a significant effect in Experimental Autoimmune Encephalomyelitis (EAE), an animal model of MS. **Aim:** The aim of this study was to assess the effects of Laquinimod on immune cell compartments and on its ability to mount humoral and cellular immune response. **Conclusions:** Even at systemic exposure much higher than being clinically tested, laquinimod preserves immune-surveillance and is associated with conservation of the ability of animals to mount a T-cell dependent humoral immune response against antigen.

**High concentration of cerebrospinal fluid neurofilament light chain is associated with impaired cortical activity during cognitive task in clinically isolated syndrome suggestive of MS**

**C. Tortorella, R. Romano, M. Ruggieri, V. Direnzo, P. Iaffaldano, M. Mastrapasqua, R. G. Viterbo, P. Taurisano, L. Fazio, T. Popolizio, G. Blasi, A. Bertolino, M. Trojano, Bari, Italy**

**Background:** Cerebrospinal fluid (CSF) neurofilament (NFL) is considered a suitable marker of neuroaxonal damage and a prognostic factor on the conversion of clinically isolated syndrome (CIS) to MS. Increased fMRI cortical activity during working memory (WM) and attention tasks have been reported in CIS suggesting early
adaptive changes of neuronal activation. **Aim:** To investigate the interaction between CSF NFL levels and neural activity during tasks of working memory and attentional control. **Conclusions:** This analysis confirms that fMRI brain activity during WM is impaired since the early stages of MS and suggests a load related impairment of attentional processing in CIS. Furthermore, these data demonstrate that cognitive related dysfunction of the DLPC in CIS is correlated to CSF NFL levels suggesting a possible role of NFL as a surrogate outcome in neuroprotective trials.

**Safety and tolerability of BG-12 in the phase 3 DEFINE trial in patients with relapsing-remitting multiple sclerosis**

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**Background:** DEFINE (Determination of the Efficacy and Safety of Oral Fumarate in RRMS), a randomized, double-blind, placebo-controlled, multicentre, phase 3 clinical trial, evaluated efficacy and safety of BG-12 over 2 years in patients with relapsing-remitting multiple sclerosis (RRMS). Results from DEFINE showed significant effects of BG-12 on all primary and secondary efficacy endpoints. **Objective:** To report safety and tolerability data from the DEFINE study. **Conclusions:** Results from the DEFINE study show that BG-12 has a favorable safety and tolerability profile over 2 years in patients with RRMS, consistent with that observed in the phase 2b study.

**Efficacy on MRI endpoints of BG-12, an oral therapy, in relapsing remitting multiple sclerosis: data from the phase 3 DEFINE trial**

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**Background:** BG-12 (dimethyl fumarate) is an experimental oral treatment for relapsing-remitting multiple sclerosis (RRMS) that may have dual anti-inflammatory and neuroprotective effects via the Nrf2 pathway. In a phase 2b trial, BG-12 reduced inflammatory activity on magnetic resonance imaging (MRI) in patients with RRMS. **Objective:** To report the effects of BG-12 on MRI efficacy endpoints in the phase 3 DEFINE (Determination of the Efficacy and Safety of Oral Fumarate in Relapsing-Remitting MS) study. **Conclusions:** The results of the MRI analysis of the DEFINE study demonstrate a potent anti-inflammatory effect on focal white matter lesions, in line with that of the more potent approved agents, and support the clinical findings with and potential of BG-12 as an effective oral treatment for patients.

**Long-term safety of mitoxantrone therapy for multiple sclerosis**

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**Background:** The long-term risk of either leukemia or cardiomyopathy after mitoxantrone therapy for multiple sclerosis has not been established. We therefore evaluated these risks after a follow-up period of up to 8.5 years. **Conclusion:** This series of patients suggests that the long-term risk of either leukemia or cardiomyopathy after mitoxantrone therapy for multiple sclerosis is low when patients are treated according to standard protocol.
Clinical outcomes for interferon-beta-1b versus placebo, 21 years following randomization
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Background: Long-term data on the effect of disease-modifying therapies on clinical outcomes in patients with multiple sclerosis (MS) are sparse. The 21-Year Long-Term Follow-Up (21Y-LTF) study identified the vital status of 98.4% (366/372) of patients who participated in the pivotal IFNB-1b trial conducted between 1988 and 1993.

Conclusions: With near-complete patient ascertainment (98.4%), an initial randomized control trial design, and the longest period of follow-up for a treatment-exposed MS population, these data provide insight into both the effects of IFNB-1b on survival/mortality in patients with MS and long-term clinical outcomes. Confirmatory findings from both active treatment groups strengthen the evidence for an effect on all-cause mortality.

Data from prolonged-release fampridine trials confirm that 20% improvement in walking speed is clinically meaningful
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Objective: The timed 25-foot walk (T25FW) is the only validated tool available to measure walking speed (WS) in patients with multiple sclerosis (MS). While changes in group performance provide information on the efficacy of treatment, it is important to know what change in WS is clinically meaningful for an individual. Studies have demonstrated that a ≥20% change in T25FW is a statistically reliable change and is related to both patients’ self-perceived change in WS and change in neurological status. We present a post hoc analysis of 2 phase 3 trials (MS-F203/MS-F204) of prolonged-release (PR) fampridine (dalfampridine extended release tablets in US) to assess the percentage of patients who showed a clinically meaningful ≥20% increase in WS on the T25FW.

Conclusions: Significantly more patients treated with PR-fampridine than placebo experienced ≥20% improvements on the T25FW. These patients also had meaningful improvements in self-reported walking disability. The ≥20% increase in walking speed is clinically meaningful in a more severely walking impaired patient population and adds to the evidence supporting this criterion for meaningful change on T25FW.

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