ECTRIMS
EUROPEAN COMMITTEE FOR TREATMENT AND RESEARCH IN MULTIPLE SCLEROSIS

Day 2

ECTRIMS 2021 Congress Reporting

Clinical

Free Communication 1: COVID-19

Thursday, 14 October 16:45 – 17:45 CEST

Speakers: Gabriel Bsteh, Thomas Frisell, Steve Simpson-Yap, Maria Pia Sormani, Susana Otero-Romero

Chairs: Maura Pugliatti, Harald Hegen

Conclusion: For the majority of patients with MS, choice of disease-modifying therapy (DMT) should continue to focus on treating MS rather than adjusting due to COVID-19. However, there is evidence for increased severity of COVID-19 infection in some patients receiving rituximab or ocrelizumab as well as lower vaccine response compared with other DMTs. As a result of a joint effort between ECTRIMS and the European Academy of Neurology (EAN), a European evidence-based consensus on vaccination in patients with MS has been developed.

What's New: An Austrian study of 171 patients with MS and a diagnosis of COVID-19 infection found that the vast majority (86%) had a mild disease course. Exposure to DMTs for MS, including immunosuppressive DMTs, was not associated with COVID-19 severity or mortality. Similarly, a Swedish study of 172 MS patients receiving rituximab found no association between cumulative lifetime dose or timing of last dose of rituximab and the odds of hospitalisation after COVID-19 infection.

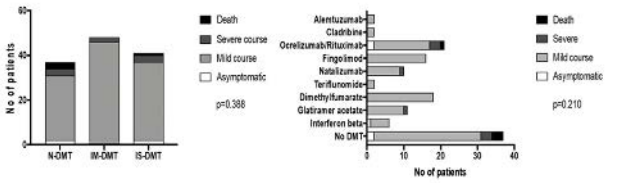
An analysis of the MS Data Alliance COVID-19 study including over 5,500 patients with suspected (17%) or confirmed (83%) COVID-19 infection looked at associations with DMTs and COVID-19 severity. In contrast to the smaller studies, ocrelizumab and rituximab were associated with higher frequencies of hospitalisations, ICU admission and requirement for artificial ventilation versus other DMTs. Furthermore, rituximab was associated with higher frequencies of death.

Data from the CovaXiMS study in Italy compared SARS-CoV-2 antibody levels before and after mRNA vaccination in 1,431 patients with MS. Patients receiving fingolimod, rituximab or ocrelizumab had lower SARS-CoV-2 antibody titres after their second vaccine dose than patients receiving other DMTs; overall, the Moderna vaccine induced three times higher antibody titres than the Pfizer vaccine in patients receiving DMTs.

Background: Certain DMTs used in MS can suppress vaccine response and increase infection risk, which has raised questions and concerns regarding the continuation and dosing interval of these treatments during the COVID-19 pandemic.

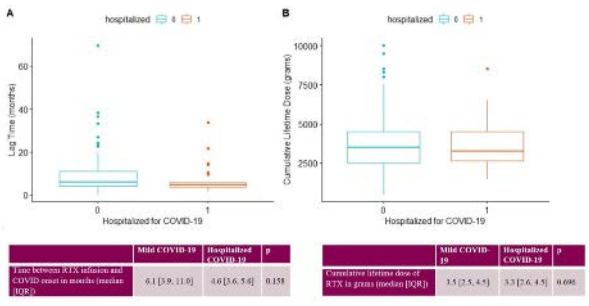
Outcome according to DMT

(Bsteh presentation)



Bsteh G, et al. (2021) COVID-19 severity and mortality in multiple sclerosis are not associated with immunotherapy: Insights from a nation-wide Austrian registry. PLoS ONE 16(7):eo255316. https://doi.org/10.1371/journal.pone.0255316

(Frisell presentation)



	Mild COVID-19	Hospitalized COVID-19	p
Time between RTX infusion and COVID onset in months (median [IQR])	6.1 [3.9, 11.0]	4.0 [3.6, 5.6]	0.158

	Mild COVID-19	Hospitalized COVID-19	p
Cumulative lifetime dose of RTX in grams (median [IQR])	3.5 [2.5, 4.5]	3.3 [2.6, 4.5]	0.696

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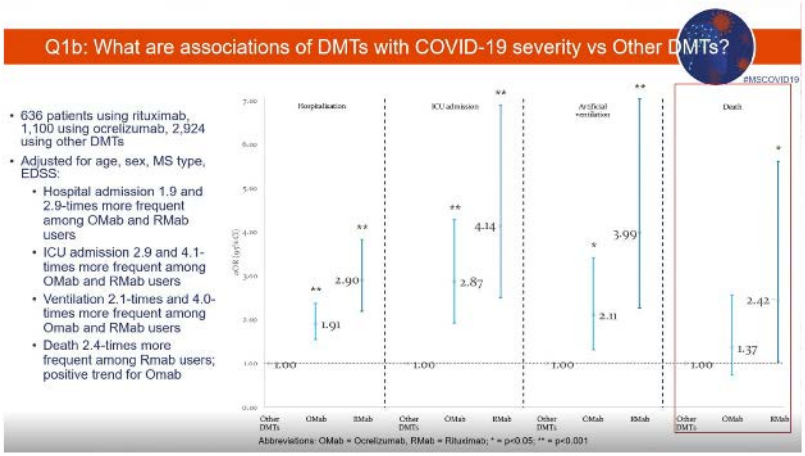
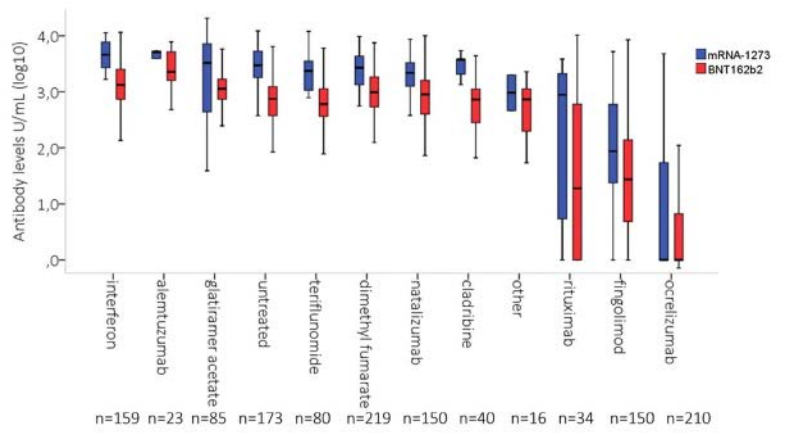
(Simpson-Yap presentation)



Antibody levels according to DMT and vaccine type

(Pia Sormani presentation)



Clinical

Poster Tour 5 - Clinical

Thursday, 14 October 18:00 – 18:45 CEST
Speakers: Gian Marco Schiavi, Paolo Preziosa, Valentina Camera, Madiha Shatila, Ingo Kleiter, Sapir Dreyer-Alster
Chairs: Harald Hegen

Conclusion: Prognostic factors such as number of cortical lesions at diagnosis, age of onset and White race are associated with poorer outcomes in MS and aquaporin-4-antibody Neuromyelitis optical Spectrum Disorder (AQ4-NMOSD). Reduction of long-term disability in paediatric patients with this disorder requires early diagnosis, careful monitoring that includes cognitive testing, and active relapse prevention. To streamline the diagnosis of MS, future revisions to the McDonald criteria should consider a single unified set of magnetic resonance imaging criteria that could be applied to both relapsing remitting MS (RRMS) and primary progressive MS (PPMS). Recent findings confirmed the long-term efficacy of satralizumab in patients with AQP4-IgG-seropositive NMOSD and highlighted the safety of COVID-19 vaccination in patients with MS, with validation of these results after booster vaccinations ongoing.

What's New: After a mean of 17.03 years of follow-up, patients who converted to secondary-progressive MS (SPMS) had a higher number of cortical lesions at diagnosis and a greater proportion had >3 lesions compared with patients who did not convert. There was a significant correlation between the number of cortical lesions at diagnosis and both EDSS and SPMS conversion.

Use of Neurite Orientation Dispersion and Density Imaging (NODDI) was explored in patients with MS versus age- and sex-matched healthy controls. Normal-appearing cortex, thalamic and normal-appearing white matter neuroaxonal loss, as well as inflammation in normal-appearing white matter, gliosis and loss of tissue coherence, were associated with cognitive impairment in MS.

Investigations into the early predictors of paediatric-onset AQP4-NMOSD found that time to first relapse was associated with onset age <12 years, and time to visual disability predictors were optic neuritis at onset and White race. Non-Asian rather than Asian children were more likely to develop motor disability. Time to cognitive impairment was shorter in patients with cerebral syndrome at onset and those with resistance to IV methylprednisolone.

A study investigating whether there is a need for separate diagnostic criteria for PPMS compared the performance of the McDonald 2017 RRMS DIS and DIT criteria with the PPMS DIS and DIT criteria in patients with suspected PPMS. RRMS DIS criteria had higher sensitivity and accuracy than the PPMS DIS criteria, and while the PPMS DIT criteria had high sensitivity, specificity was much lower than the RRMS DIT criteria. When combined, the sensitivity, specificity and accuracy for RRMS and PPMS were very similar.

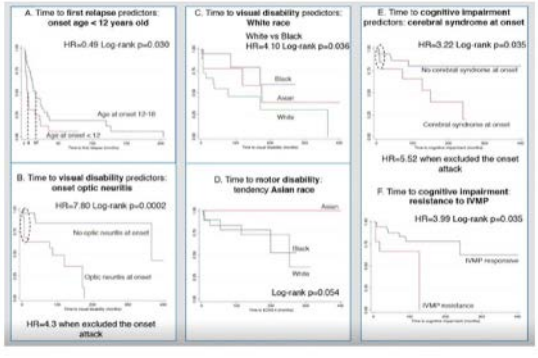
In the open-label extension phases of SAkuraSky and SAkuraStar, the efficacy of satralizumab in AQP4-IgG-seropositive NMOSD was sustained in the long term (median exposure ~4 years). The annualised relapse rate remained consistently low in satralizumab-treated patients, and the favourable safety profile seen in the double-blind period was sustained in the long term, with no new safety findings up to 7 years of follow-up.

Recent data revalidate the safety of COVID-19 vaccination in patients with MS. The adverse event profile of the Pfizer vaccine in patients with MS did not differ from that in vaccinated healthy subjects, with the most common adverse events being

MRI results in patients with or without SPMS conversion
(Schiavi presentation)

** p<0.001 * p<0.05	All	RRMS+CIS	SPMS	PPMS
N. CLs	2,26±2.29	**1,16±2.33 (**)**	**6,28±3.48 (**)**	4,63±2.07
0 CLs	103 (49.8%)	**99 (61.9%) (**)**	**3 (7.7%) (**)**	1 (12.5%)
1-3 CLs	48 (23.2%)	**45 (28.1%) (**)**	**3 (7.7%) (**)**	0 (0.0%)
>3 CLs	56 (27.0%)	**16 (10.0%) (**)**	**33 (84.6%) (**)**	7 (87.5%)
Spinal Cord	111 (53.6%)	78 (48.8%) (*)	28 (71.3%) (*)	5 (62.5%)
No Spinal	96 (46.4%)	82 (51.2%) (*)	11 (28.2%) (*)	3 (37.5%)
0 WMLs	9 (4.3%)	8 (5%) (*)	1 (2.5%) (*)	0 (0.0%)
1-3 WMLs	30 (14.5%)	29 (18.1%) (*)	1 (2.5%) (*)	0 (0.0%)
4-10 WMLs	89 (42.9%)	71 (34.3%) (*)	13 (33.3%) (*)	5 (62.5%)
>10 WMLs	79 (38.2%)	52 (32.5%) (*)	24 (61.5%) (*)	3 (37.5%)

Survival analysis results
(Kleiter presentation)

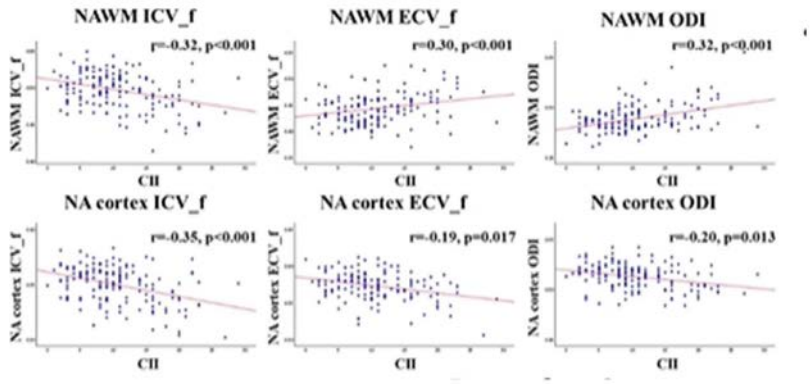


injection site pain, fatigue and headache. Younger age (18–55 years), a lower disability score (EDSS ≤3), and treatment with immunomodulatory drugs were factors associated with a higher frequency of adverse events. In the period immediately after the first dose, 1.5% of patients self-reported an acute relapse; within 4 months of the second vaccine dose, 3.1% of patients had an acute relapse versus 4.6% of non-vaccinated patients.

Background: Research into prognostic factors in central nervous system diseases and confirming the long-term efficacy of newer treatments is key to improving outcomes in patients with these diseases. The COVID-19 pandemic has highlighted the vulnerability of individuals with underlying diseases, emphasizing the importance of vaccine safety data in these populations.

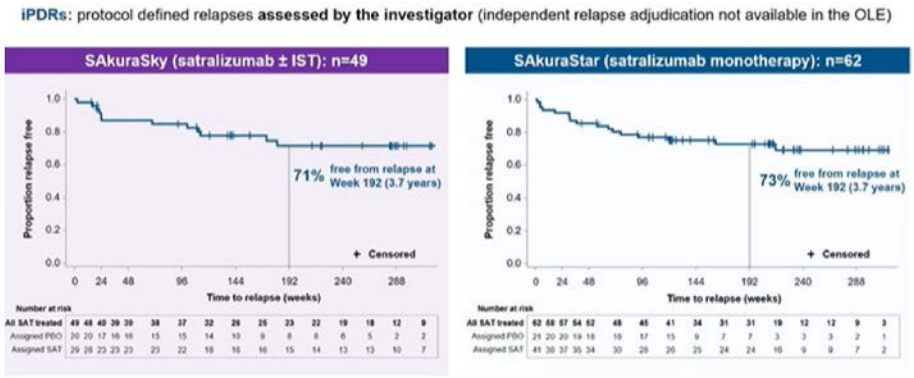
Association of microarchitecture abnormalities with cognitive impairment

(Preziosa presentation)



Long-term efficacy of satralizumab

(Kleiter presentation)



Clinical

Scientific Session 5: IMSCOGS

Thursday, 14 October 12:00 – 13:30 CEST

Speakers: John DeLuca, Bruno Brochet, Jiri Motyl, Stefano Ziccardi, Olga Marchesi, Tommy A.A Broeders

Chairs: Iris-Katharina Penner, Daniela Pinter

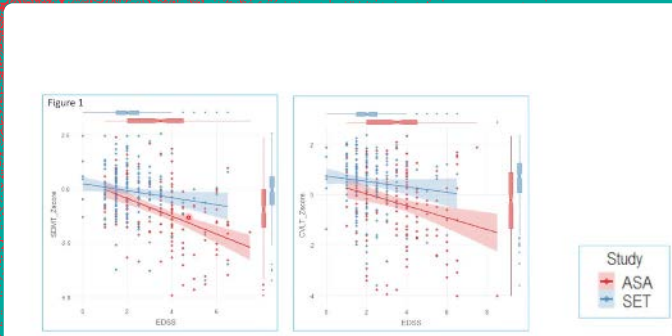
Conclusion: Cognitive assessment in patients with MS needs to become standard practice. Both information processing speed (IPS) and learning/memory should be assessed, and follow-up implemented as necessary. There are consistent data to support the effectiveness of cognitive rehabilitation in improving function. Long-term systematic assessment of real-world cohorts of patients with MS provide valuable data on cognitive impairment progression. Early cortical lesion evaluation should be conducted in patients with MS to improve diagnosis and treatment.

What's New: A re-evaluation of the original Avonex-Steroids-Azathioprine (ASA; early phase of relapsing MS) and Study of Early IFN-ß1a Treatment (SET; newly diagnosed patients) cohorts, after 19 and 10 years of follow-up, respectively, was conducted to identify cross-sectional parameters explaining cognitive outcomes. Brain parenchymal fraction, normalised grey matter volume and age were identified as the best parameters explaining the Symbol Digit Modalities Test (SDMT) results. The only parameter explaining the California Verbal Learning Test 2nd Edition (CVLT-II) score was the study cohort (ASA/SET). These results suggest that the influences of MS on verbal learning and memory are subtle.

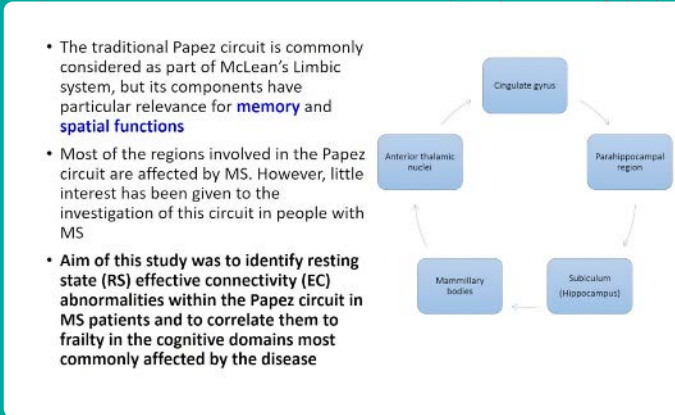
The number of cortical lesions at diagnosis of MS can accurately predict the risk of developing cognitive impairment at later stages of the disease.

Widespread resting state effective connectivity abnormalities were observed within the Papez circuit in MS patients. Abnormal anterior cingulate cortex-to-thalamus resting state effective connectivity within the left hemisphere contributed to the explanation of the worse cognitive performance in these patients.

Preceding analysis
(Motyl presentation)



Background and aims
(Marchesi presentation)

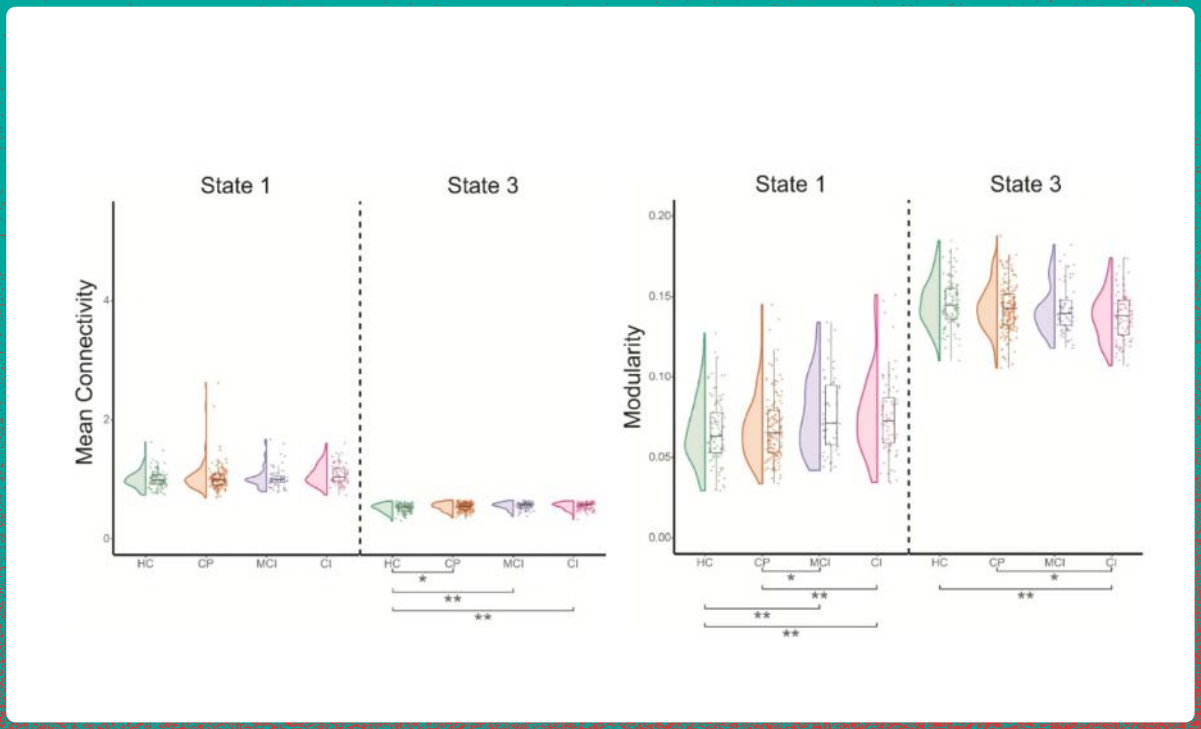


Background: The two main cognitive impairments in MS are IPS and learning/memory. Neuropsychological testing is the gold standard for assessing cognitive impairment, which tends to increase over the course of the disease. Of the three approaches to the treatment of learning and memory deficits, cognitive rehabilitation improves function through enhancing neuroplasticity and functional brain changes, whereas no conclusive data support the effectiveness of exercise or physical activity/fitness or pharmacological therapies.

Cortical lesions reflect brain damage from the early stages of MS, and are associated with clinical disability. However, prognostic data about the role of early cortical lesions with reference to long-term cognitive impairment are still missing.

The functional network is thought to play a key role in the development of cognitive impairment in MS, along with altered network dynamics. Cognitive impairment is related to less dynamic switching between network states, more time in low connectivity, high modularity and less time in between-network connectivity.

Brain States: Connectivity per Group
(Broeders presentation)



Clinical

Scientific Session 8: Paediatric inflammatory demyelinating CNS disorders

Thursday, 14 October 15:00 – 16:30 CEST

Speakers: Kevin Rostásy, Brenda Banwell, Omar Abdel-Mannan, Wendy Vargas, Chiara Curatoli, Ilya Ayzenberg

Chairs: Barbara Kornek, Silvia Tenembaum

Conclusion: Paediatric-onset MS is no less severe than adult-onset disease, and ability to function may be impaired in these children. Approximately one-third of paediatric patients with MS demyelination events test positive for serum myelin oligodendrocyte glycoprotein (MOG) antibodies. Retinal atrophy in those with optic neuritis can be thus used as an additional diagnostic parameter to differentiate myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) from MS. Social networks of children with MS are less likely than those of healthy children to promote unhealthy behaviours.

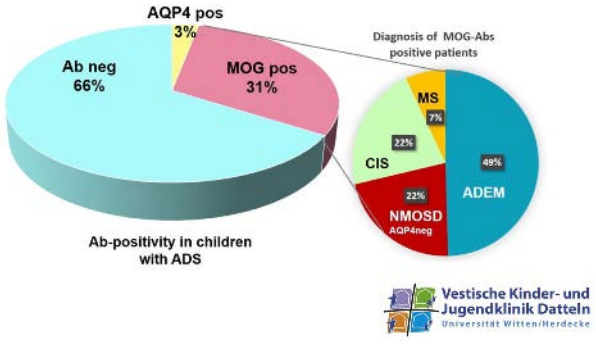
What's New: A much higher proportion of children (>30%) than adults who present with a primary demyelinating event test positive for serum MOG antibodies. In paediatric patients, each optic neuritis event is associated with substantially more pronounced retinal atrophy in children with MOGAD than in those with MS.

Patients with paediatric-onset MS are at risk for cognitive impairment and reduced employment as well as physical disability by mid-adulthood. A study found that teenagers with MS have an average IQ, with the coding subtest being the most commonly failed component (by one-fifth of patients).

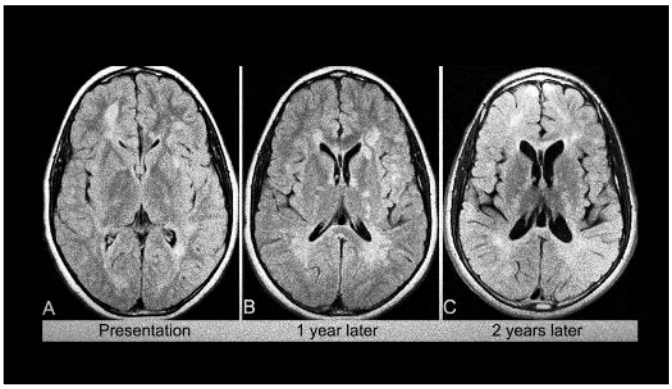
Children with MS have smaller social networks than healthy children; their social networks are more likely to be inhabited by family rather than friends/peers and less likely to include members who exert a negative influence.

Background: In contrast to adults, acquired demyelinating syndromes in children are usually monophasic and remain so in the long term, with relapsing syndromes including MS and MOGAD. Furthermore, MS and MOGAD are the most prevalent disorders associated with optic neuritis in children. Paediatric-onset MS has a relapsing-remitting phenotype in nearly all cases, with neurodegeneration evident in even the youngest patients. Social networks could affect cognitive and academic outcomes in adolescents with paediatric-onset MS.

30% of all children presenting with a 1. Demyelinating event have serum MOG abs
(Rostásy presentation)



Neurodegeneration in Pedriatric MS
(Banwell presentation)



Pathogenesis

Poster Tour 6: Pathogenesis

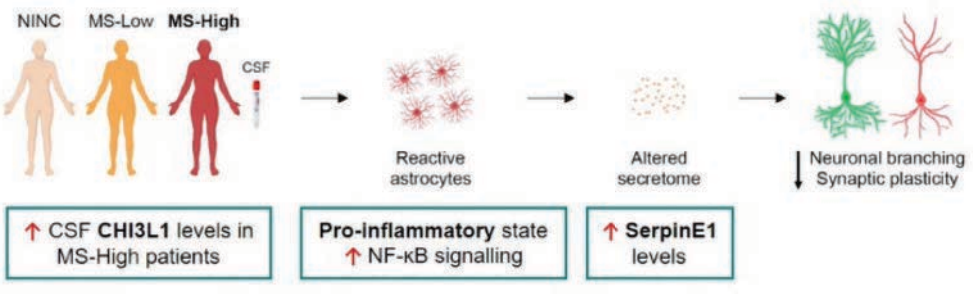
Thursday, 14 October 18:00 – 18:45 CEST
Speakers: Kenichi Serizawa, Mattias Bronge, Steven Koetzier, Clara Matute-Blanch, María Schroeder-Castagno, Irini Papazian
Chairs: Tobias Zrzavy

Conclusion: Findings presented at ECTRIMS 2021 revealed important new insights into disease pathogenesis in MS.

What's New: A new mouse model of neuromyelitis optica spectrum disorder (NMOSD) has been developed with potential applications in pathogenesis research. This model used intradermal immunisation of aquaporin-4 (AQP4) to induce clinical signs of paralysis. Mice showed NMOSD-like pathogenesis such as perivascular loss of GFAP/AQP4, complement deposition and the presence of AQP4-IgG autoantibodies. CD4+ T-cells are recognised as key drivers of MS but gaps still exist in the known autoantigen repertoire. Research using T-cell reactivity screening has unearthed four novel central nervous system (CNS) autoantigens in MS. These encephalitogenic T-cell targeted autoantigens were: FABP7, PROK2, RTN2 and SNAP91. Although autoreactive profiles were found to be heterogenous and individual, T-cell autoreactivity may have possible diagnostic utility in MS. Research undertaken to pinpoint T-cell subsets that drive the pathogenesis of MS has identified a key role for brain-homing T-helper (Th) cells. Specifically, MDR1+ Th17.1 cells were shown to be pathogenic and associated with MS disease activity - delineating them as a promising biomarker and therapeutic target in MS. Th17.1 cells are enriched in the CNS of MS patients and their activity during pregnancy is predictive of a post-partum relapse. In vitro research has shown that astrocytes exposed to a high inflammatory MS microenvironment induced non-cell-autonomous neuronal dysfunction. Specifically, astrocytes exposed to cerebrospinal fluid from MS patients with high inflammatory activity displayed an altered pro-inflammatory secretome and acquired a specific pro-inflammatory reactive state characterised by an enhanced pro-inflammatory signature, mainly associated with NF-kB signalling. Translational research has revealed an impaired capacity of neutrophils from AQP4+ NMOSD patients to undergo cell death in response to phorbol myristate acetate (PMA). Yet, initial events leading to apoptosis were increased and NETosis markers were not altered. These findings indicate that the deficient response of blood neutrophils to cell death stimuli differentiates AQP4-IgG seropositive NMOSD from myelin oligodendrocyte glycoprotein antibody-associated patients. Findings from a mouse model of chronic demyelination have demonstrated the induction of premature cell senescence (CS) of non-neuronal cells in the corpus callosum white matter that is associated with motor impairment. Natural ageing accelerated the development of CS and motor dysfunction induced by chronic demyelination. Further studies are warranted to decipher the functional relevance of the senescent cell types in the pathology of MS.

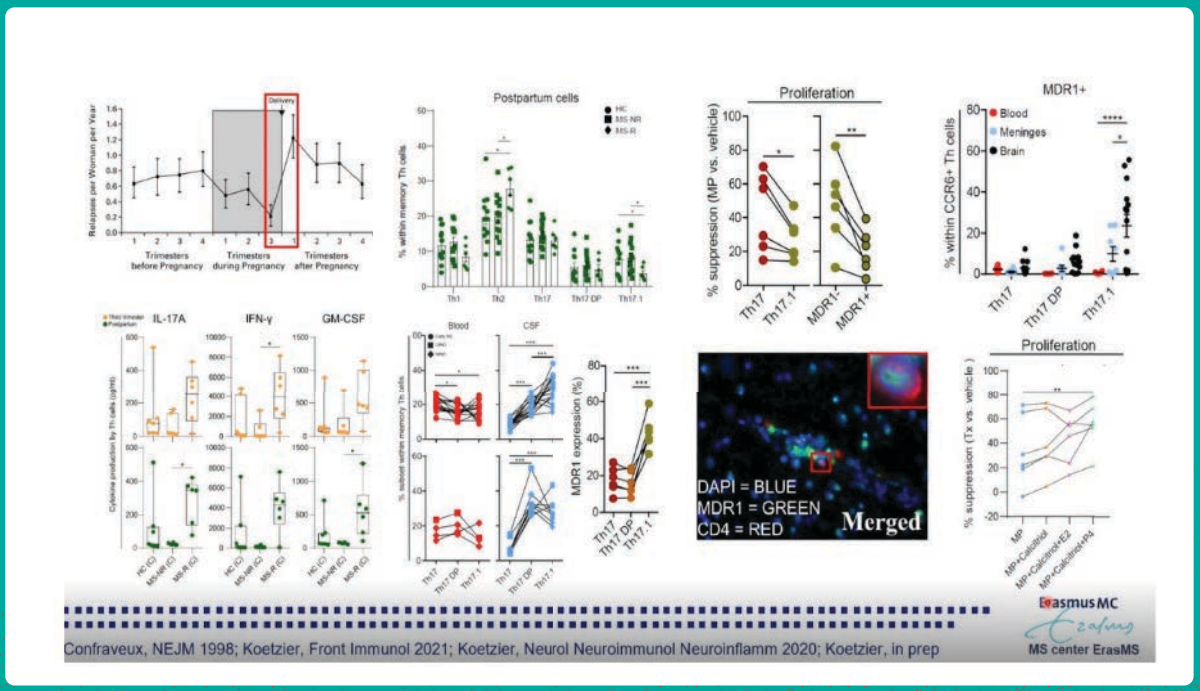
Background: Translational research in MS is vital to further knowledge about underlying pathobiological mechanisms that lead to disease development, as well as to pinpoint new targets for potential therapeutic intervention.

Astrocytes pre-exposed to CSF from MS patients with an inflammatory phenotype exhibit a reactive phenotype
(Matute-Blanch presentation)



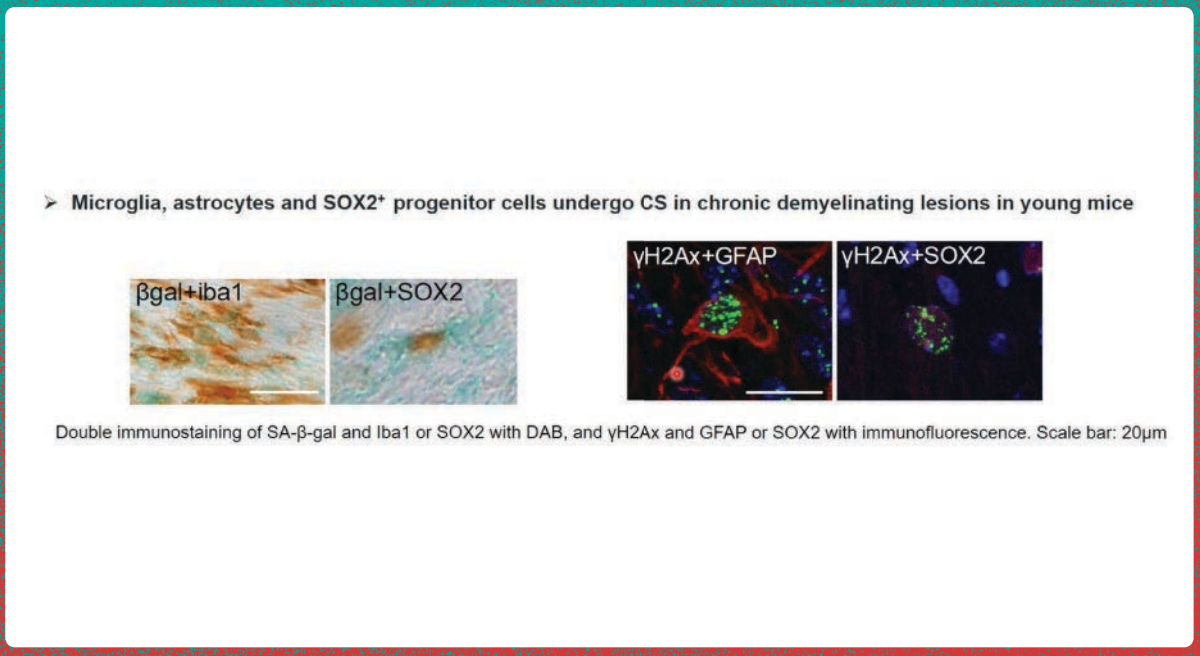
MDR1+Th17.1 cells are pathogenic and associate with MS disease activity

(Koetzier presentation)



Chronic demyelination-induced cell senescence is responsible for motor impairment in a model of MS

(Papzian presentation)



Pathogenesis

Scientific Session 9: Genetics and Epigenetics

Thursday, 14 October 15:00 – 16:30 CEST

Speakers: Chris Cotsapas, An Goris, Ali Manouchehrinia, Marijne Vandebergh, Maria Pia Campagna, Antonino Giordano

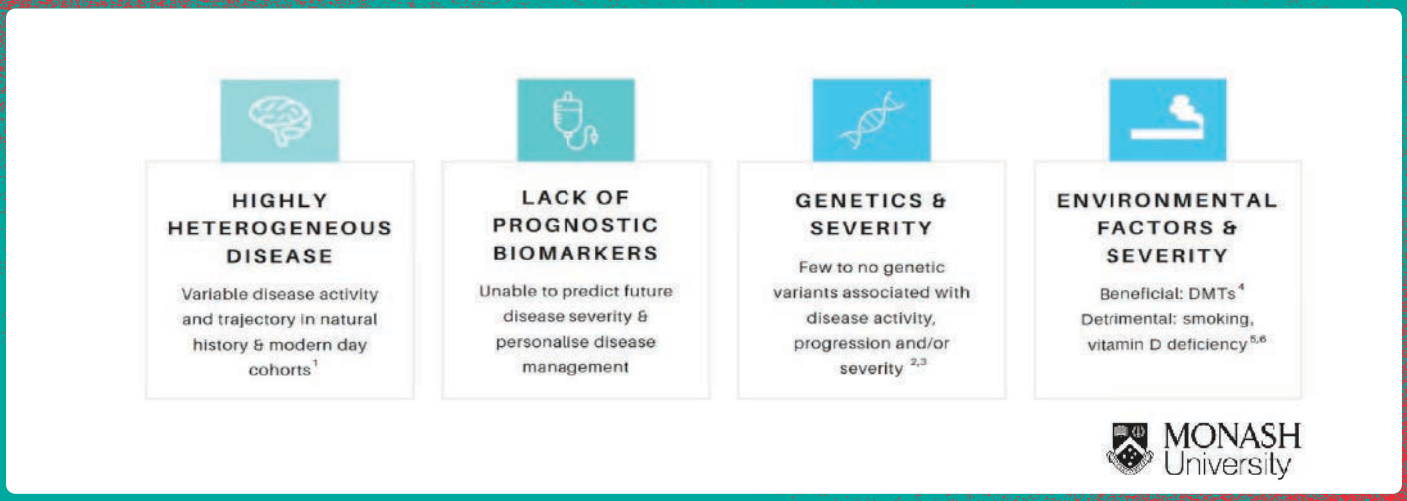
Chairs: Stephen Sawcer, Alexander Zimprich

Conclusion: To address the outstanding challenges that remain in MS genetics and epigenetics we need to build on the three key principles underpinning our current level of understanding: knowledge, technology and international collaboration. New research in this field has shown that whole blood methylation may have a potential role as a future prognostic biomarker in MS and has highlighted genetic variants which are risk factors for disease relapse.

What's New: In a study using Swedish ancestry data (1986–2019), familial risk estimates did not differ noticeably for two subtypes of MS (primary progressive or relapsing) at disease onset, in line with null findings reported in genome-wide association studies (GWAs). Application of GWAs to longitudinal data identified an association between genetic variation in WNT9B and a more than doubling the hazard ratio for relapse. Hazard of relapse in MS was associated with a protective role of naturally occurring higher vitamin D levels but not with genetically related increases in body mass index.A study using samples and methylation data from the MSBase registry found that whole blood methylation was associated with disease severity in relapse-onset MS and accurately predicted disease severity.Gene set analysis in a study of 480 MS patients revealed a possible involvement of iron homeostasis in neurodegeneration. Specifically, the rs16902359_T allele was associated with a lower probability of having a primary progressive disease course.

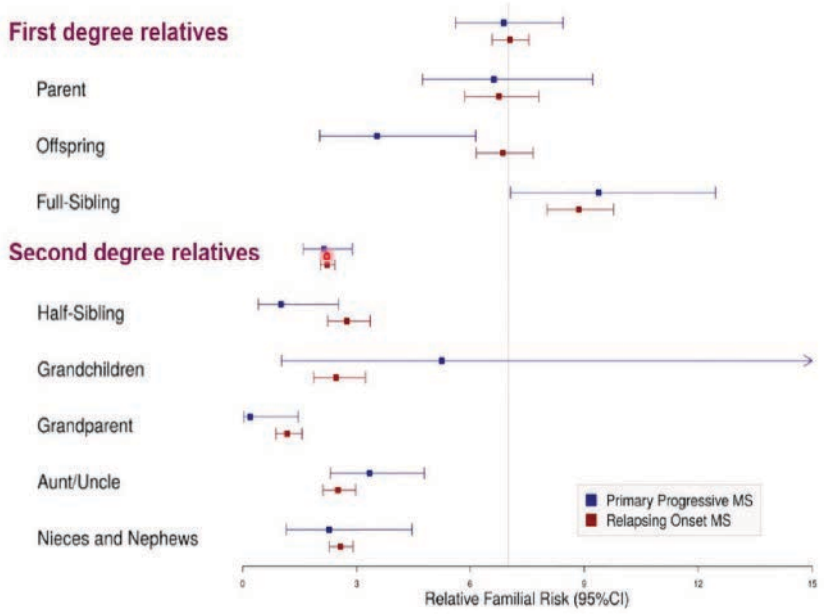
Background: MS risk is heritable. Of the total heritable fraction of MS, approximately 20% can be explained by findings to date – namely common variants identified through GWAs – while around 5% are rare variants. The remaining 75% cannot be accounted for by individual associations, underscoring the need for larger genetic studies to fill the current gap in understanding: other important challenges remain to be addressed in the field of MS genetics. These include: the fine mapping and understanding of the mechanism of action of risk variants; deeper exploration of the genetic architecture of MS; and, moving beyond susceptibility to heterogeneity.

Multiple sclerosis. Disease severity
(Campagna presentation)



Similar familial risk and heritability in relapsing and progressive onset MS

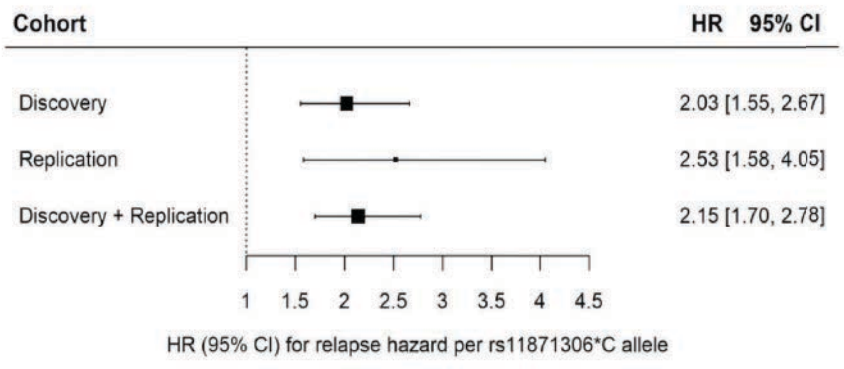
(Manouchehrina presentation)



Karolinska Institutet

Genetic variation in WNT9B more than doubles the hazard for a relapse

(Vandebergh presentation)



Pathogenesis

Hot Topic 5: Role of astrocytes in inflammatory demyelinating CNS disease

Thursday, 14 October 12:00 – 13:00 CEST

Speakers: Veit Rothhammer, Claudia Lucchinetti, Francesco Quintana

Chairs: Manuel Comabella, Irena Lavrnja

Conclusion: Pharmacologically manipulating the astrocyte response may serve as a new avenue for therapeutic intervention in both MS and neuromyelitis optica (NMO). Evidence supports a potential role for the astrocyte transforming growth factor (TGF)-α/vascular endothelial growth factor (VEGF)-B/aryl hydrocarbon receptor (AHR) axis as a biomarker in MS. The spectrum of astrocytic morphological changes in NMO attests to the complexity of actors that influence the range of astrocytic physiological responses to a targeted attack by aquaporin-4 (AQP4)-specific IgG. As well, EphrinB3-EphB3 signalling inhibitors are under development for the therapeutic control of astrocytes and microglia in neurological disorders.

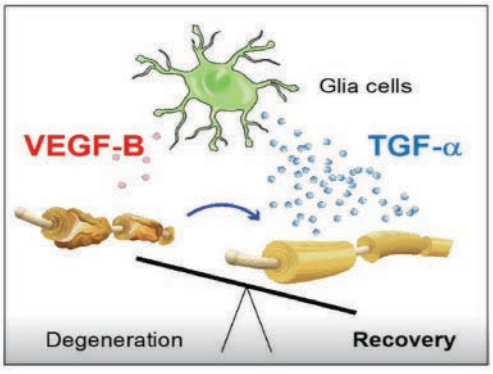
What's New: The AHR in astrocytes mediates tissue-protective effects. Microglia-derived TGF-α/VEGF act as potential upstream regulators for astrocytes and inversely modulate astrocyte activation. Both the TGF-α/VEGF-B ratio and AHR ligand levels are reduced in MS patients versus controls and have been shown to correlate with disease severity. AHR ligand levels are also predictive for conversion from clinically isolated syndrome (CIS) to definite MS.

Research suggests that astrocytes also play a role in NMO, driven by astrocyte responses to pathogenic AQP4-specific antibodies. Astrocytic alterations beyond demyelinating lesions are consistent with astrocytopathy being an early and primary event in evolving NMO lesions. NMO targeting the AQP4 water channel is a global astrocytopathy not simply definable by demyelination and astrocytic lysis.

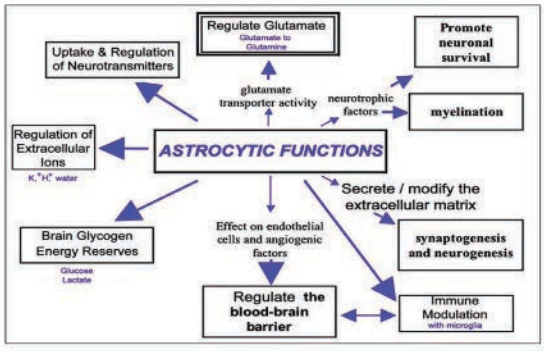
RAPID-seq, a new technique for studying cell interactions in vivo has revealed a novel type of physical astrocyte-microglia interaction during central nervous system (CNS) pathology. EphrinB3-EphB3 signalling participates in a bidirectional astrocyte-microglia communication which promotes CNS inflammation and neurodegeneration. A38 - a novel inhibitor of EphB3 kinase activity - is the lead molecule in clinical development in this therapeutic arena.

Background: When peripheral immune cells enter the CNS in MS they trigger additional mechanisms of pathology for which therapeutic tools are not currently available. These pathobiological mechanisms are driven primarily by microglia and astrocytes and contribute to the development of progressive disease. Astrocytes perform multiple homeostatic functions associated with the maintenance of neurones and the structural integrity of the blood brain barrier. Astrocytes also gain additional pathogenic functions during the course of MS, including recruitment of monocytes to the CNS, activation of myeloid cells in the CNS, neurotoxicity and control of myelination/remyelination.

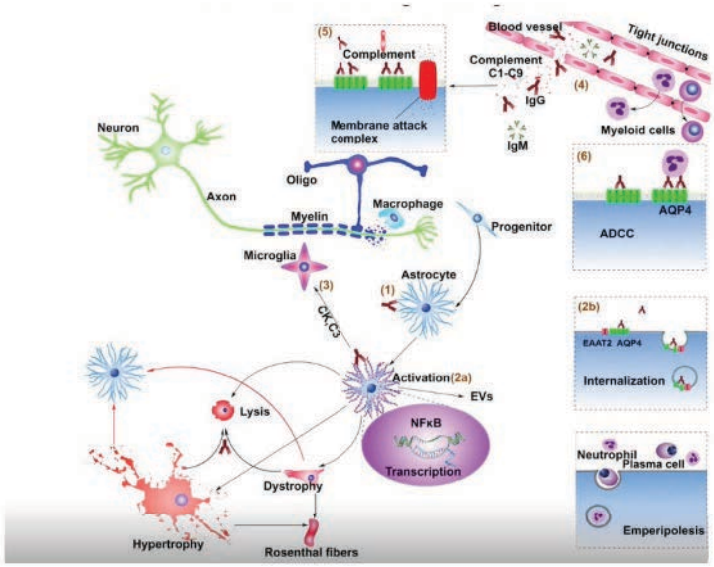
Is the astrocyte TGF-α / VEGF-B / AHR axis a potential biomaker in Multiple Sclerosis?
(Rothhammer presentation)



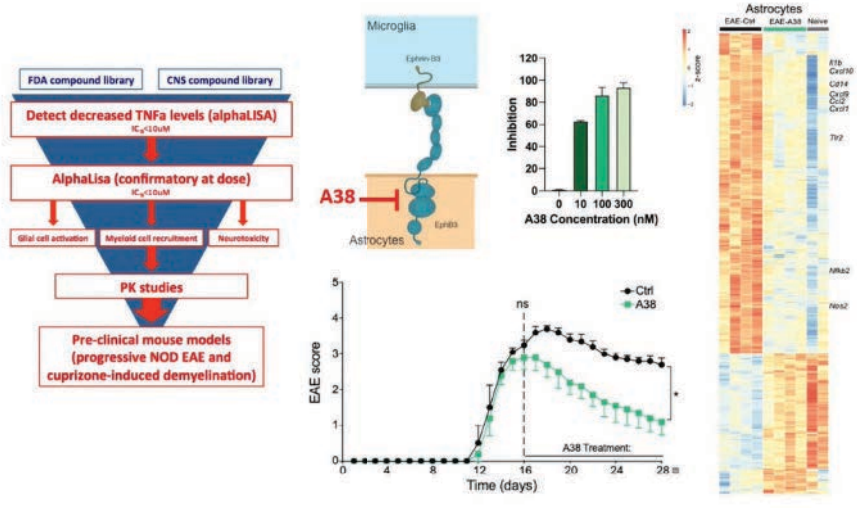
Astrocytes: support the metabolic and trophic maintenance of normal neuronal function
(Lucchinetti presentation)



Proposed pathways to astrocytopathy in NMO from observations of human immunohistopathology, and in vitro and in vivo effects of AQP4-IgG on live glial cells
(Lucchinetti presentation)



A novel inhibitor of EphB3 kinase activity reduces CNS pathology
(Quintana presentation)



Pathogenesis

Hot Topic 8: Neurodegeneration in demyelinating CNS diseases

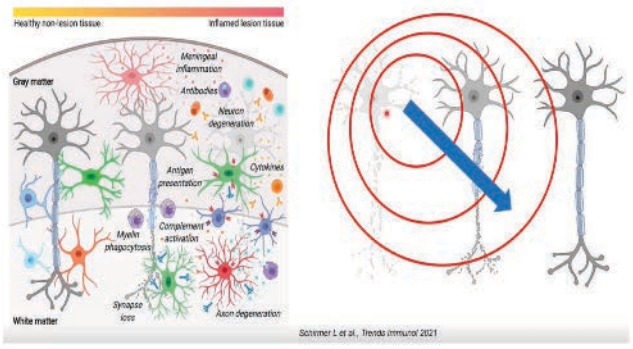
Thursday, 14 October 16:45 – 17:45 CEST
Speakers: Izumi Kawachi, Lucas Schirmer, Catherine Lubetzki
Chairs: Sonja Hochmeister, Nikos Evangelou

Conclusion: As yet, no positive Phase 3 clinical trial results have been achieved for regeneration in MS. Remyelination remains an active field of translational research in MS and several clinical trials are ongoing. New targets under evaluation to prevent neurodegeneration in MS include both oligodendroglial and microglial targets.

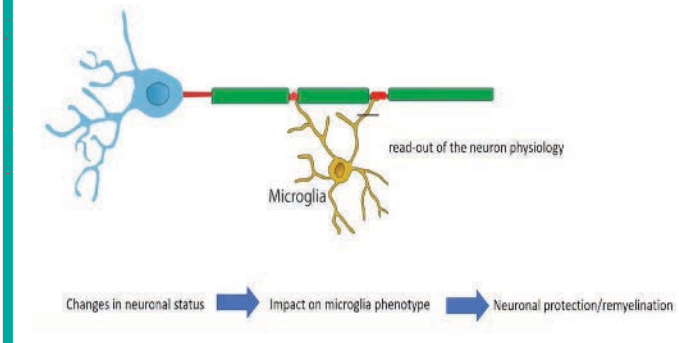
What's New: Regeneration is an active area of therapeutic research in both MS and optic neuritis, with many Phase 2 clinical studies underway and new biomarkers being explored. New targets for regeneration in MS are also emerging. These include the possibility of rejuvenating aged oligodendrocyte precursor cells (OPCs) either by overcoming brain stiffness-induced reduction of OPC activity, by reducing food intake or by giving metformin to rejuvenate OPCs. The other approach involves targeting microglia, a key cell type for remyelination, to boost their pro-regenerative function. The aim of therapeutic intervention is therefore to promote a pro-regenerative phenotype. The contact point between the microglia and the node of Ranvier also appears to be a reciprocal interaction involved in health and disease and may have therapeutic potential in neuronal protection/ remyelination.

Background: MS is associated with neuronal vulnerability and multilineage diversity. However, natural neuronal variability and the huge number of different types can make it difficult to decipher underlying pathogenesis, particularly in the spinal cord. Neurone subtype pathology is linked to cortical demyelination and meningeal inflammation. Subpial excitatory projection neurones exhibit the highest level of transcriptomic vulnerability. Glial cells transform into various reactive subtypes characterised by immune and stress transcripts. Myeloid cells also show a high level of subtype reactivity with the presence of phagocytosing myelin transcripts.

Sequence of immune-mediated neuronal damage
(Schirmer presentation)



Microglia-nodes contacts: a reciprocal interaction in health and disease
(Lubetzki presentation)



Clinical trials targeting remyelination
(Lubetzki presentation)

Remyelination : an active field of translational research

	Population	Mechanism of action	Status	Patients (ITT)	Results (or outcomes for ongoing studies)	
GNbAC1[105]	RRMS	Monoclonal antibody against HERV	Completed	270	Negative for primary MRI outcome	+
GSK239512[106]	RRMS	Histamine H_3 receptor antagonist	Completed	131	Small effect on MTR	
Opicinumab[107]	RMS	Anti-LINGO1 monoclonal antibody	Completed	419	Negative for clinical outcomes	
Bexarotene (EudraCT 2014-003145-99)	RMS	RetinoidX receptor γ agonist	Completed	50	Partially positive	+
Opicinumab (NCT03222973)	RMS	Anti-LINGO1 monoclonal antibody	Completed		Negative	0
Domperidone (NCT02493049; open-label)	RRMS	Increases serum prolactin	Completed	24	Results pending (MRI measures of lesion repair)	
Opicinumab[108]	Acute optic neuritis	Anti-LINGO1 monoclonal antibody	Completed	82	Negative	
Clemastine fumarate[109] (crossover)	Chronic optic neuritis	Anti-histaminic	Completed	50	Reduced VEP latency	+
Clemastine fumarate (NCT02521311)	Acute optic neuritis	Anti-histaminic	Ongoing	..	VEP latency	
Transorbital electrical stimulation (NCT04047361)	Acute optic neuritis	Stimulation-induced repair	Ongoing	..	VEP latency	
Transorbital electrical stimulation (NCT03862313)	Acute optic neuritis	Stimulation-induced repair	Ongoing	..	Retinal nerve fibre layer	
Nanocrystalline gold (NCT03536559)	Chronic optic neuritis	Myelin gene transcription	Ongoing	..	VEP latency	
Bazedoxifene (NCT04002934)	Chronic optic neuritis	Oestrogen receptor modulator	Ongoing	..	VEP latency	

RR-MS or RMS

Optic neuritis

From Lubetzki et al, Lancet neurology 2020

Clinical trials targeting neuroprotection
(Lubetzki presentation)

DRUG	phase	patients	outcomes	Positive Negative	reference
Ibudilast	2	255	Brain volume	positive	Fox et al 2018
(MS SMART) Fluoxetine, Amiloride, Rilyuzole	2	393 multiarm	PBFV	negative	Chataway 2020
EPO in RRMS	2	52	Composite clinical score	negative	Schreiber 2017
Biotin	3	642	% patients with improvement	negative	Cree 2020
Lipoic acid	2	51	PBFV	positive	Spain 2017
Lamotrigin	2	120	Brain volume	negative	Kappor 2010
High dose statins	2	140	Annualized brain atrophy	positive	Chataway 2014
EPO ON	3	100	RNFL	negative	unpublished
Phenytoin ON	2	86	RNFL	positive	Raftopoulos 2016

Optic neuritis

Imaging & Non-Imaging

Hot Topic 6: Biosensors in MS – the future has started

Thursday, 14 October 12:00 – 13:00 CEST
Speakers: Johannes Lorscheider, Jennifer Graves, Tanuja Chitnis
Chairs: Patrick Altman, Tjalf Ziemssen

Conclusion: Methodological rigour is required for the successful adoption of biosensing devices into MS clinical trials. The features that will determine the most successful devices are retest repeatability and sensitivity to change over short time periods. Although the use of consumer wearables and smart phones should improve the availability and scalability of biosensor-based measurements, there remain a significant number of challenges associated with biosensor monitoring for MS in real-world environments (e.g., for data collection in patient registries). These include the evaluation and optimisation of appropriate standardised devices, as well as comprehensive validation; the advancement of data extraction and analysis techniques; fit, aesthetics and technology challenges; considerations of privacy and security; medicolegal considerations; ethics approvals; and cost implications.

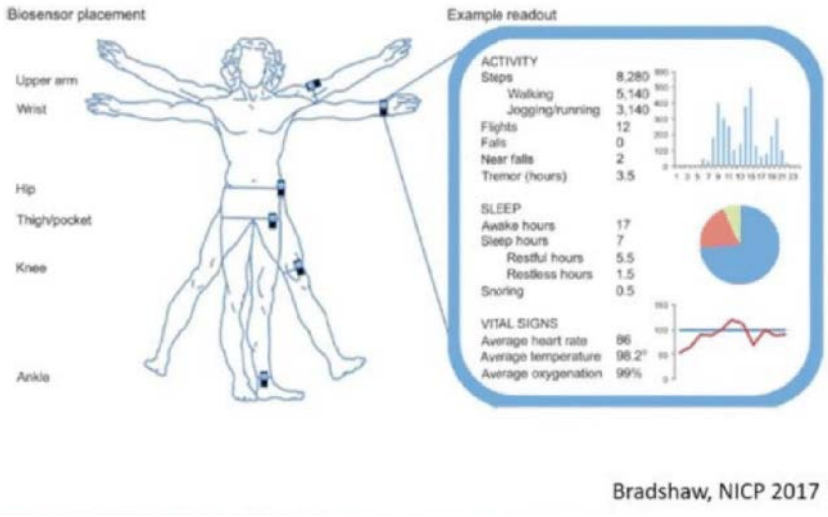
What's New: Accelerometers, which sense linear displacement, are currently the most common biosensors used in MS, with 80% of MS biosensing studies focusing on accelerometry. However, other sensors are rapidly being incorporated into devices and clinical trial outcomes in MS based on technology leveraged from non-health sectors, e.g., interactive Android and iOS apps, the gaming and computer industries. Other sensors include gyroscopes, photoplethysmography, surface electromyography (EMG), electrodermal sensors and touch screens. Exoskeletons for mobility and physical activity have been evaluated and trials are planned of multi-sensors with an accelerometer, gyroscope and surface electromyography, as well as eye-tracking to monitor MS progression. Beyond clinical trials, biosensing may be used for real-world monitoring of symptoms, motion, events and autonomic symptoms in patients with MS between office visits, e.g., via use of wearable biosensors or motion capture in the home. A recent Verily smart watch research study investigated the correlation of biosensor metrics with standard clinical measures of MS disease in the clinic and the free-living environment. The study found that multiple walking, turning and balance features showed specific Spearman correlations with disease severity in the clinic. Several of the walking and turning features were measurable in the free-living environment.

Background: Digital biosensors convert a physical or biological event into a measurable signal, which is then converted directly into digital data within the device. Biosensing can address unmet needs in the neurological examination and clinical monitoring of people with MS, particularly the accelerated need for home monitoring driven by the COVID-19 pandemic. Active biosensing, in which the user is asked to perform a specific known test paradigm, eases the development and refinement of algorithms, but is less representative of actual performance and has lower temporal resolution. Passive biosensing, in which data are collected during usual daily activities, is likely a better reflection of actual performance, but it's more challenging to develop algorithms and interpret results with passive biosensing and there are potential privacy issues.

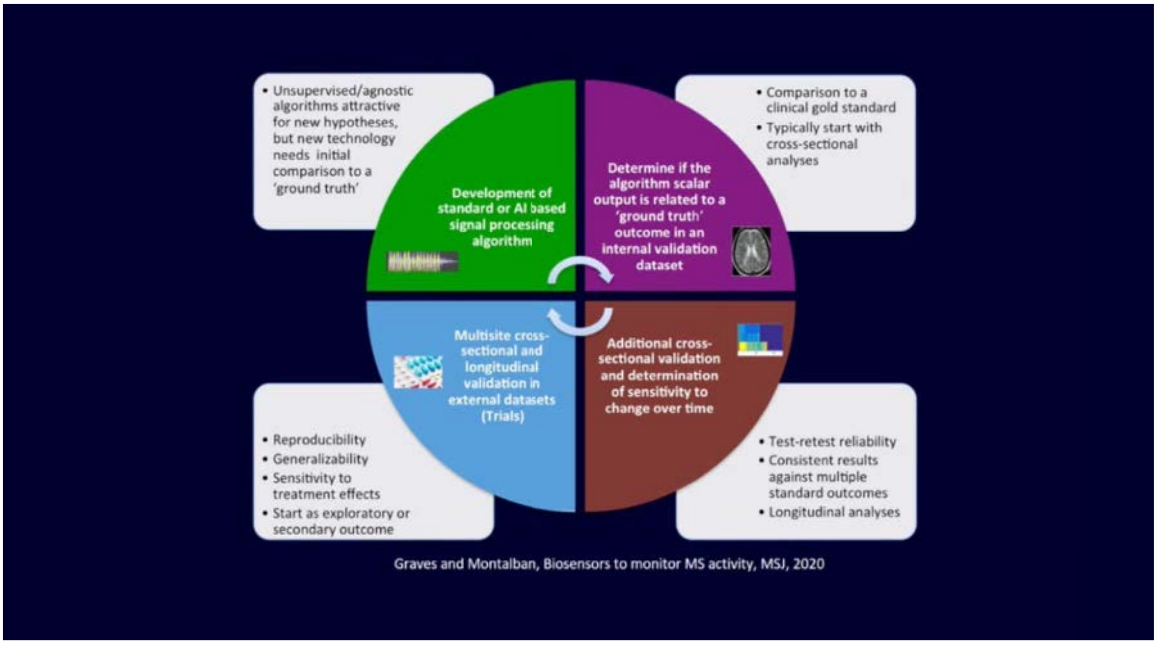
Beyond accelerometers
(Lorscheider presentation)

Sensor	Measurement	Potential use	Availablility in consumer devices
Gyroscope	Angular velocity	Improves accuracy of accelerometer data, fall detection, tremor	+++
Photoplethys-mograph (PPG)	Heart rate	Activity tracking, fatigue	+++
Surface EMG	Muscle activity	Movement	+
Electrodermal sensors	Skin conductivity	Stress, fatigue	+
Touch screen		Cognitive testing, dexterity testing, key stroke dynamics	+++

Wearable biosensor devices for monitoring symptoms/mobility
(Chitnis presentation)



Validation of new biosensor assesments
(Graves presentation)



Imaging & Non-Imaging

Scientific Session 10: Body-fluid biomarkers

Thursday, 14 October 15:00 – 16:30 CEST

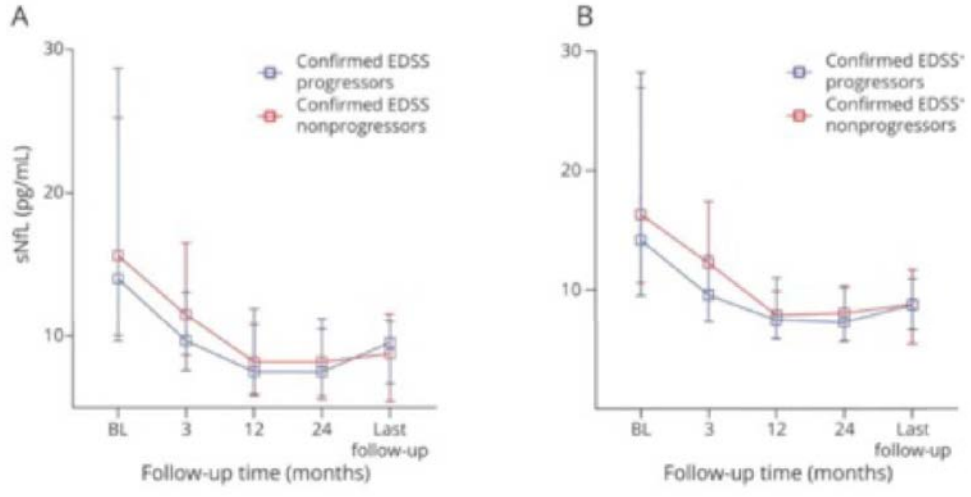
Speakers: Jens Kuhle, Charlotte Teunissen, Claire Bridel, Elias Sotirchos, Tianrong Yeo, Arlette Bruijstens

Chairs: Georgina Arrambide, Michael Khalil

Conclusion: The presented data indicate that serum neurofilament light (sNfL) may be ready for routine clinical use as a biomarker in MS, with several specific recommendations for use. Although associations have been found between sNfL measurement, short-term brain atrophy and new T2 lesion development, further follow-up work is needed to assess the impact on longer-term radiological outcomes and brain substructures. In a cohort of relapsing-remitting MS (RRMS) patients, sNfL appeared to lack the sensitivity to reflect the lower rate of sustained neurodegenerative axonal damage that underlies progression in RRMS. Interestingly, observations from a delayed-type hypersensitivity (DTH) MS rat model study suggested that metabolomics should be explored as biomarkers to detect early subclinical neuroinflammation in MS patients. Future studies should explore other potentially interesting cerebrospinal fluid (CSF) proteins of higher abundance in paediatric MS patients, as CSF protein expression is highly age-dependent, as well other promising disease progression and prognostic biomarkers.

What's New: Evidence suggests that sNfL shows a physiological age-dependent increase; however, fixed cut-offs should not be used as they may lead to misleading interpretations or loss of power. Normative data from a general population allows us to discern pathological from physiological changes in sNfL, which is an important step towards individual use. Studies have shown that Z-scores and percentiles are very similar, but Z-scores are more sensitive to longitudinal changes, which is important in detecting subtle increases in sNfL, e.g., in progression. An internet-based application for the generation of sNfL Z-scores is currently being developed. However, one study that examined the associations of sNfL in the MS PATHS network with longitudinal brain atrophy and new T2 lesion development found that a single baseline sNfL measurement was associated with short-term retrospective and prospective brain atrophy and T2 lesion development. These associations appeared to be consistent across MS disease subtypes and demographic groups. Furthermore, a recent, prospective, observational study evaluated the association between sNfL

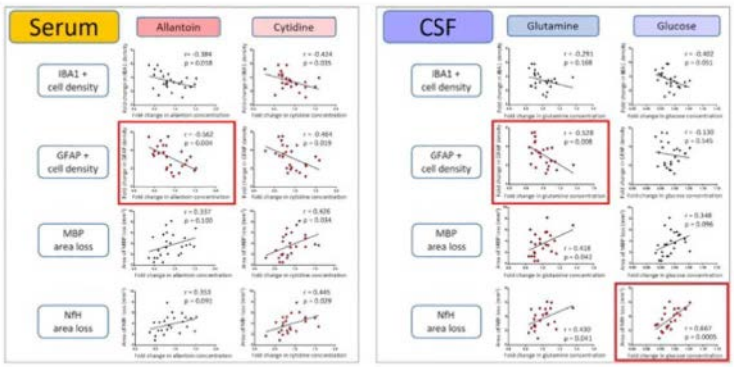
Longitudinal dynamics of Neurofilament Light
(Bridel presentation)



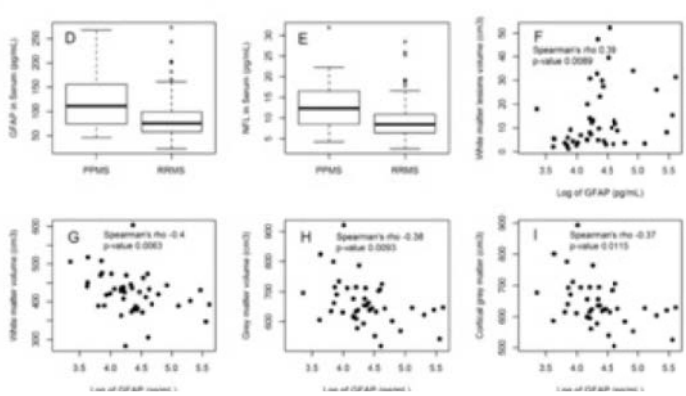
levels and Expanded Disability Status Scale (EDSS) disease progression in patients with RRMS treated with natalizumab. The longitudinal dynamics of sNfL did not differ between EDSS progressors and non-progressors and baseline NfL levels did not have prognostic value for EDSS progression. An animal study, using the delayed-type hypersensitivity (DTH) MS rat model, which produces a focal, clinically silent lesion, explored the nature and temporal dynamics of CSF and sNfL levels as well as metabolomics across DTH lesion evolution and correlated them with histological markers of neuroinflammation. The study found that levels of these metabolites (serum – allantoin and cytidine; CSF – glutamine and glucose) correlated with histological markers of neuroinflammation and tissue damage. Furthermore, carboxypeptidase E, known to be involved in central nervous system (CNS) formation and neuroprotection, and semaphorin 7A, which is involved in immune cell regulation and CNS formation, de- and regeneration have been identified as potential biomarkers of interest for predicting progression to paediatric-onset MS. Recent studies also position glial fibrillary acidic protein (GFAP) as an emerging blood biomarker in MS, as a relationship has been observed between GFAP and MRI changes. Furthermore, CNTN1 and Olink-candidates have been identified as promising candidates for additional disease progression and prognostic biomarkers.

Background: Neuro-axonal injury and degeneration is the main driver of persisting disability in MS. It happens early in the disease course and can be measured in CSF and blood. Neurofilaments are highly specific neuronal proteins that are very stable in-vitro and, although there are currently no validated biofluid markers in clinical use in MS, NfL is a first-in-class measure of disease activity and treatment response in MS showing great promise. sNfL levels are associated with clinico-radiological measures of inflammatory disease activity and are predictive of future disability worsening and brain/spinal cord atrophy. However, evaluation of sNfL in large, heterogenous MS populations is limited. One key question is whether NfL can be used to monitor or predict progression in MS, as it is known that sNfL is associated with acute focal inflammation and levels of NfL increase in the blood of MS patients undergoing a relapse and return to baseline levels within weeks/months of the acute event. A second question is whether serum and CSF metabolomics may detect clinically-silent neuroinflammatory lesions earlier than NfL. Moreover, interesting CSF proteins more highly abundant in paediatric-onset MS compared with paediatric monophase acquired demyelinating syndromes (mADS) may be important biomarkers in predicting which paediatric patients will progress to paediatric-onset MS, the most common relapsing ADS. Overall, it is acknowledged that other biomarkers are needed to support early diagnosis, prognosis and monitoring in MS.

Correlation metabolites and histology
(Yeo presentation)



Correlation metabolites and histology
(Teunissen presentation)



Imaging & Non-Imaging

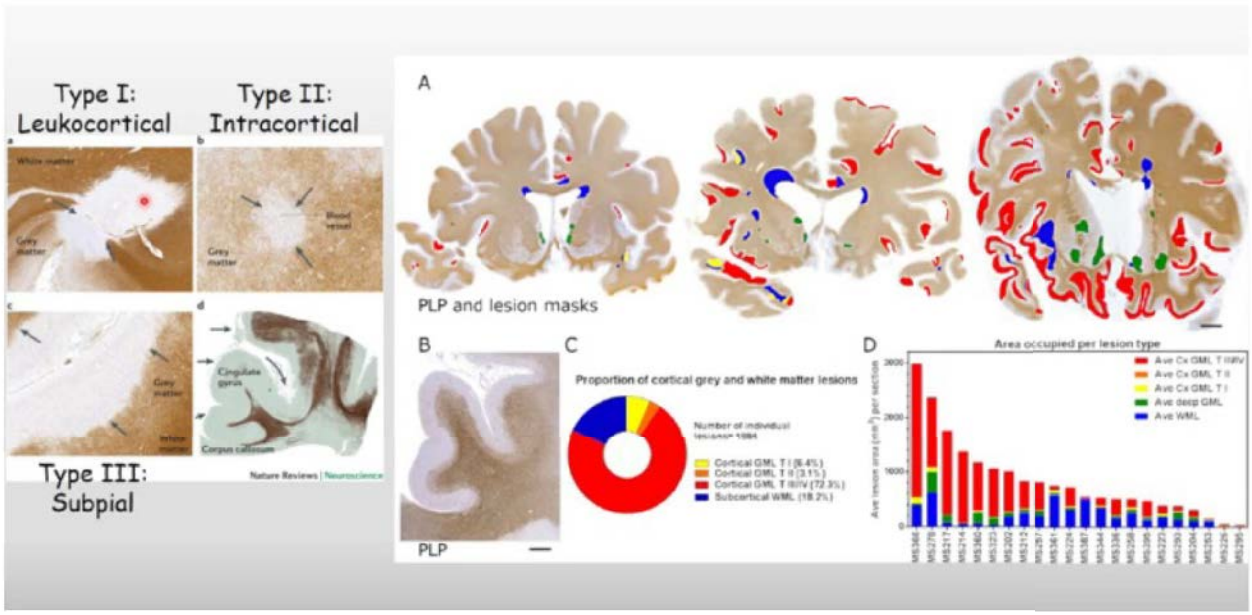
Hot Topic 10: Cortical demyelination – a key factor in disease progression

Thursday, 14 October 16:45 – 17:45 CEST
Speakers: Richard Reynolds, Jeffrey Bennett, Roberta Magliozzi
Chairs: Christine Stadelmann-Nessler, Simon Hametner

Conclusion: Therapeutic targets that could reach the central nervous system space to inhibit cellular inflammation should be investigated for the treatment of MS. Potential targets include inhibitors of CXCL-13 or BAFF and depleting targets against plasma cells or against CCR2+ monocytes, including proteasome inhibitors. Necroptosis represents a cell death pathway that is amenable to therapeutic intervention to ameliorate neuronal injury and atrophy. In-vivo surrogate markers of meningeal inflammation and cortical demyelination are required for more rapid MS diagnosis and prognosis (and monitoring). Cerebrospinal fluid (CSF) biomarkers are potentially the best in-vivo surrogate markers of meningeal inflammation and multiple biomarkers will likely be required to predict disease progression.

What's New: Cortical demyelination is evident in early MS and has inflammatory features. Multiple studies, undertaken to investigate the molecular mechanisms underpinning this meningeal inflammation, have identified that the factors driving cortical demyelination are cellular and soluble. Cellular inflammation is prominent in the meninges and CD8 T-cells and plasma cells may play an early role. Amongst soluble factors, TNF-α and IFN-γ are paramount to drive inflammation. Complement may play multiple roles and understanding the impact of complement activation may depend on the model system. Pro-inflammatory cytokines, antibodies and even exosomes produced by meningeal B-cells may play a role. One study of the molecular mechanism of meningeal inflammation found that several cytokines are highly upregulated, in particular CXCL-13, IFN-γ, TNF and LT-α. The role of LT-α was further investigated in an animal model, which showed that chronic elevation of CSF LT-α for three months stimulated subpial demyelination and neuronal loss (as seen in the cerebral cortex in MS cases), although neuronal loss was not dependent on demyelination. Combined neuropathology-molecular imaging profiling of cortical lesion pathology in MS has demonstrated that a common inflammatory CSF protein profile may reflect cortical pathology both at the time of death and at the time of diagnosis and predict disease activity after four years of follow-up.

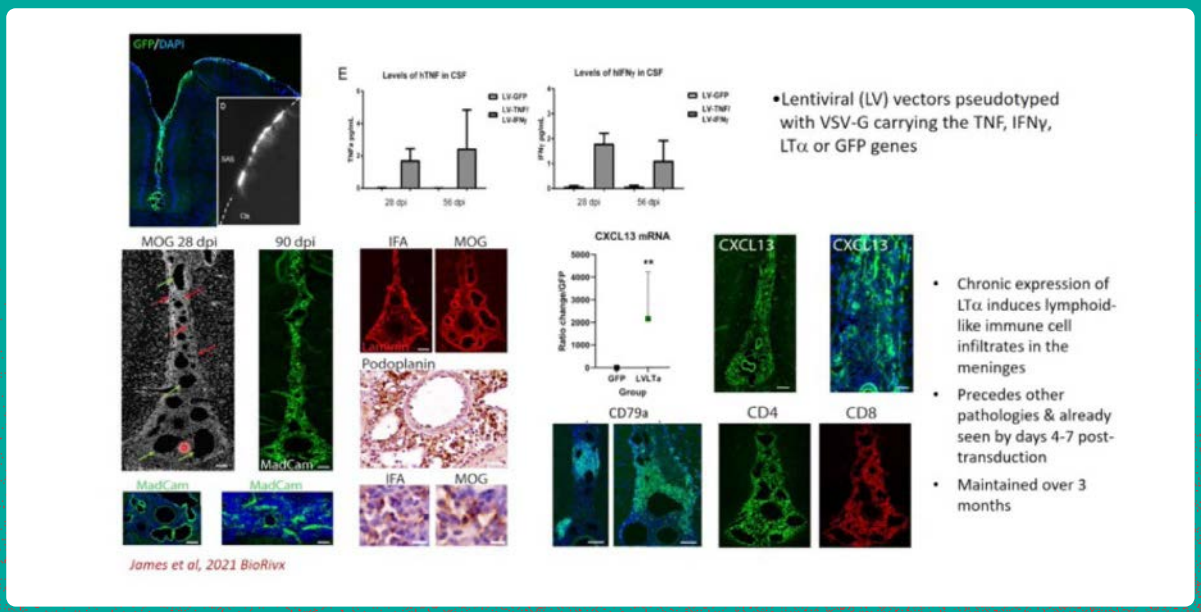
Subpial cortical grey matter lesions are the most frequent and occupy the greatest area
(Magliozzi presentation)



Background: It is well accepted in MS that grey matter (GM) pathology (particularly in the cerebral cortex) is as extensive, if not more extensive, than white matter (WM) pathology. Although not much of the cortical pathology is visible on brain MRI, it is characterised by several cellular pathologies, including meningeal infiltration. Cortical GM demyelination in MS is not restricted to any one cortical region; however, most demyelination is subpial (Type III lesions) and demyelinated lesions are larger in the cortical sulci. Subpial cortical demyelination is unique to MS and therefore is likely to inform on disease-specific pathology relevant to MS patient care. Many studies have shown that leptomeningeal infiltrates, characterised by lymphoid-like tissue formation, are a common feature of progressive MS. There is a continuum, with increasing meningeal inflammation associated with increasing cortical pathology. Neuronal loss is one of the main consequences of meningeal inflammation, showing a clear outside-in gradient related to meningeal inflammation, with pyramidal neurons being highly susceptible to loss. GM pathology is clinically relevant as GM lesions and/or atrophy are associated with MS motor deficits and cognitive impairment. Extensive cortical damage at onset is associated with florid inflammatory clinical activity and predisposes to a rapid occurrence of the progressive phase.

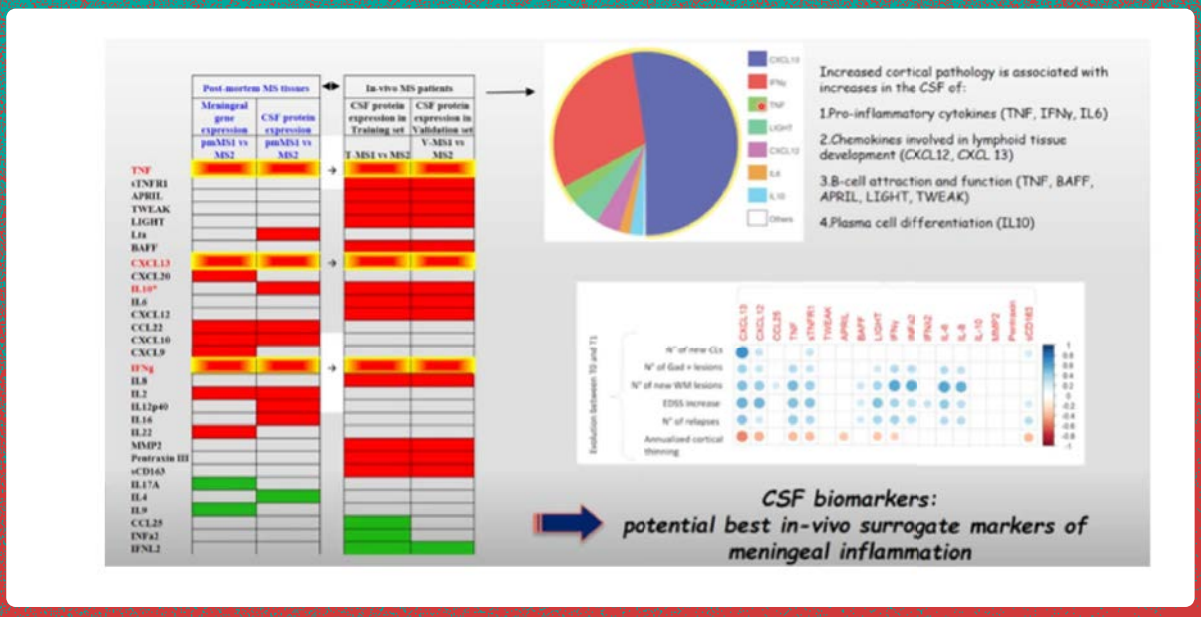
Chronic elevation of CSF lymphotoxin-α for 3 months stimulates lymphoid tissue development

(Reynolds presentation)



A common inflammatory CSF protein profile may reflect cortical pathology both at death and at time of diagnosis and predict disease activity after 4 years of follow-up

(Magliozzi presentation)



Imaging & Non-Imaging

Poster Tour 7: Imaging and non-imaging biomarkers / translational

Thursday, 14 October 18:00 – 18:45 CEST

Speakers: Bastien Caba, Nevin A John, Douglas L Arnold, Jaume Sastre-Garriga, Lindsay Ross, Elisa Colato

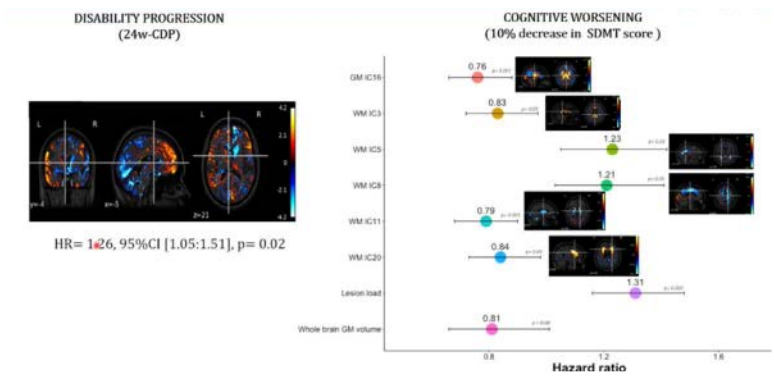
Chair: Krysztof Selmaj

Conclusion: Standardised sT1w/T2w ratio maps can help in future clinical trials to identify participants with MS more likely to progress. In addition, subject to further validation, identifiable pathological changes detectable by machine-learning (ML) using radiomic features from pre-lesion normal-appearing white matter (NAWM) could potentially be used for risk stratification in MS and as exploratory endpoints in clinical trials. With respect to biomarkers, decreased total N-acetyl-aspartate (tNAA), reflecting reductions in neuroaxonal integrity and mitochondrial dysfunction in NAWM in the earliest stages of MS, is associated with long-term disability. Furthermore, a reduced spinal canal area is a significant contributor to disability, even when adjusted for brain and spinal cord disease burden and demographic variables, and using a range of different outcomes. Moreover, associations between MS symptoms and hypothalamic subregional volumes (HSVs) have been identified, although initial findings on the differences in direction of these associations warrant further evaluation. Finally, the findings of a long-term suppression of magnetic resonance imaging (MRI) disease activity study support the use of early treatment with ocrelizumab in reducing disease activity in patients with relapsing MS (RMS) and primary-progressive MS (PPMS).

What's New: In the first study, 17 white matter (WM) and 6 grey matter (GM) patterns of sT1w/T2w covariance were identified in participants with secondary-progressive MS (SPMS). Data-driven WM and GM patterns that predicted Expanded Disability Status Scale (EDSS) progression and cognitive worsening were identified using routinely available sT1w/T2w ratio maps. In a separate study, an ML method demonstrated relatively high and generalisable performance across populations at different stages of MS for prediction of lesion formation. This highlights the nature of lesion formation in MS, which seemingly arises from areas of NAWM that may contain pathological changes detectable using ML techniques. A long-term disability study using proton magnetic resonance spectroscopy and MRI measures in patients with clinically isolated syndrome (CIS) determined that tNAA levels measured at CIS onset were lower in those who developed MS or moderate-severe disability at 15 years compared with those who remained CIS. In a separate study, cross-sectional and clinical radiological data from the MSPATHS-network prospective cohort were used to confirm the hypothesis that a larger spinal canal area is associated with a lower level of disability in MS. This lends support to the existence of a spinal cord reserve and extends to the spinal cord the concept of brain reserve, as initially described in Alzheimer's research. A further study in patients with MS who completed a standard protocol MRI with seven days of clinical visits found that MS symptoms (i.e., fatigue, depression and sleep disturbance) were associated with HSVs, although the directions of these associations differed. Finally, an open label extension (OLE) study showed that patients with MS receiving ocrelizumab maintained near-complete suppression of focal MRI disease activity. Advantages gained by those initially randomised to ocrelizumab in long-term reduction of T2 and T1 lesion formation, as well as global/regional volume loss, tended to persist in RMS and PPMS.

Background: Predicting disability in progressive MS is a major challenge. Several recent studies have investigated the predictive value of WM and GM patterns from disability and cognitive worsening in SPMS, as well as exploring associations between early metabolic changes, spinal cord canal area volume or HSVs with disability and/or symptoms in MS. For MS patients, new lesions on T2 brain MRI are a marker of acute inflammatory disease activity and evidence suggests that abnormalities exist within the NAWM more than two years prior to lesion formation. One recent study developed a ML-based algorithm able to predict new T2 lesions up to 48 weeks prior to their emergence, using cross-section T1- and T2-weight brain MRI data from the NAWM. A further study assessed the long-term suppression of MRI disease activity and reduction of global/regional volume after switching to/maintaining ocrelizumab therapy in the OLE period of two Phase III studies (OPERA I/II and ORATORIO).

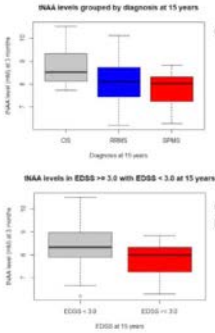
(Colato presentation)



(John presentation)

Results

Baseline differences in tNAA



(ANOVA, p=0.001)

(t-test, difference -0.64, p<0.01)

Association between baseline tNAA levels and EDSS ≥ 3.0 at 15 years

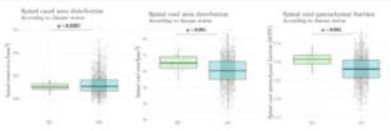
Characteristic	Odds ratio	95% CI	p
tNAA (mM)	0.32	0.12 - 0.73	0.011
T2LV (mL)	1.51	1.04 - 2.26	0.029
NBV (cm^3)	1.00	0.99 - 1.01	NS
Brain GEL number	0.90	0.73 - 1.20	NS
Spinal cord lesion number	3.96	1.95 - 9.84	<0.001

C-statistic = 0.90
All patients with EDSS (n=89)

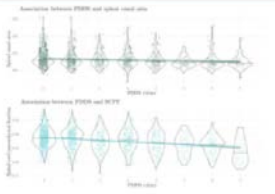
(Sastre-Garriga presentation)

Age and sex-adjusted linear regression models

- ✓ **SCA** (β=-4.8; 95% CI: -7.3, -2.1; p = 0.0002) **lower** in patients
- ✓ **SCPF** (β=-0.03; 95% CI: -0.04, -0.02; p < 0.0001) **lower** in patients
- ✓ **No differences in SCcA** (β=2.6; 95% CI: -0.7, 5.9; p = 0.125)



Box plot of SCcA, SCA and SCPF according to disease status. All p values presented here are obtained with a univariate Mann-Whitney test. MS (Multiple Sclerosis), HC (Healthy Control)



Violin plots showing the association between Patient Determined Disease Steps (PDDS) and Spinal Canal Area (above) / Spinal Cord Parenchymal Fraction (SCPF) (below).

Patient Determined Disease Steps. SCcA was independently predictive of **PDDS** (β=-0.12; 95% CI: -0.21, -0.03; p = 0.012) together with SCPF, T2 lesion volume and age. The model displayed an R^2 of 0.19.

Neuro-QoL upper and lower extremities domains. SCcA was independently predictive of **Lower Extremity Function** (β=0.82; 95% CI: 0.31, 1.32; p = 0.016) together with SCPF, T2 lesion volume and age. SCcA was not independently predictive of **Upper Extremity Function** (β=0.36; 95% CI: -0.13, 0.85; p = 0.152) nor it was sex; SCPF, T2 lesion volume and age were independently predictive.

MSPT components. SCcA was not independently predictive of **WST, MDT** nor **CST, but** was independently predictive of **PST** (β=0.80; 95% CI: 0.22, 1.38; p = 0.007) together with SCPF, T2 lesion volume and age.

(Caba presentation)

Results

- Feature selection yielded 40 features: 18 from T1, 22 from T2; 22 from the "core", 18 from the "periphery".
- The model achieved 66.4% balanced accuracy, 66.5% precision, 66.0% sensitivity, 66.8% specificity and 72.6% area under the curve on the ADVANCE validation set.
- The corresponding ASCEND testing-set metrics were 64.6%, 63.7%, 68.0%, 61.2%, and 71.4%, respectively.

Figure 3: Prevalence of Each Variable in the Selected Set of 40 Radiomic Features Used for Discriminating Between NAWM Patches That Will and Will Not Lead to a New T2 Lesion Emergence

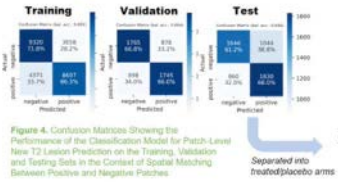


Figure 4. Confusion Matrices Showing the Performance of the Classification Model for Patch-Level New T2 Lesion Prediction on the Training, Validation and Testing Sets in the Context of Spatial Matching Between Positive and Negative Patches

Separated into treated/placebo arms

Note: Colormap represents number of patches, not percentage values.

Biomarkers/Translational Therapy

Hot Topic 7: Disease modifying treatment – if and when to stop?

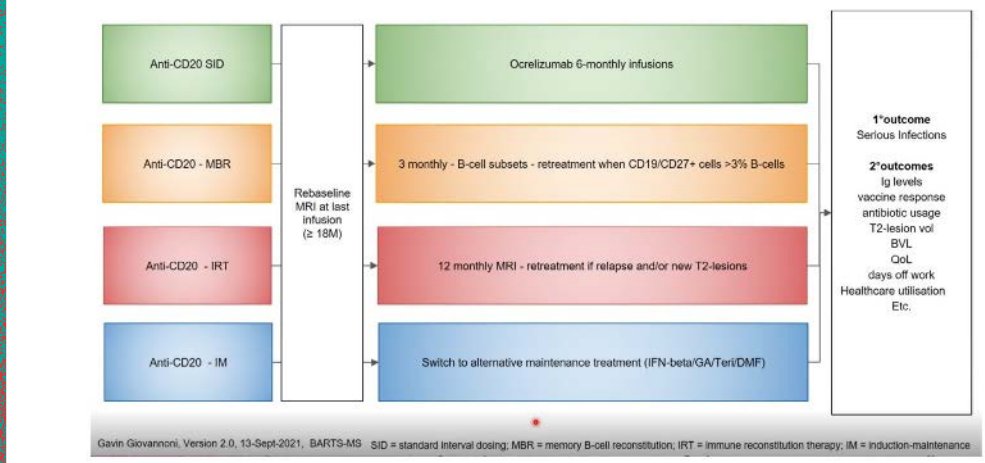
Thursday, 14 October 12:00 – 13:00 CEST
Speakers: Ilya Kister, Gavin Giovannoni, Deborah Miller
Chairs: Anat Achiron, Gabriel Bsteh

Conclusion: Stopping disease modifying therapies (DMTs) in patients younger than 45 years is not advisable, but the risk of relapse is low after stopping injectable DMTs in older patients with stable disease. New data are required to support de-risking treatments in older patients by timely stopping and switching of DMTs. Furthermore, new methodologies are needed to analyse data from registries and apply the findings at the level of the individual, not only the group level, to better understand patient outcomes following treatment discontinuation.

What's New: Patients aged 45 years and above with a single lifetime relapse and no disease activity for over 5 years have been reported to have a low risk of disease activity after stopping an injectable DMT. Similarly, patients with progressive disease and no relapses over 5 years may not need to continue receiving injectable DMTs, and the ADIOS-IM study has been designed to investigate adaptive dosing with anti-CD20 therapies. Clinicians should go beyond magnetic resonance imaging (MRI) and relapse data when assessing disease activity. Immunosuppression is not recommended in older patients due to supressed vaccine response and immunosenescence leading to increased risk of infection, and MS progression tends to slow in older age which can reduce the need for DMTs. Deciding to stop a DMT should be a collaborative process between patients and their healthcare providers, based on the risk tolerance of both parties. It is important to maintain a care plan once routine monitoring associated with a DMT has stopped.

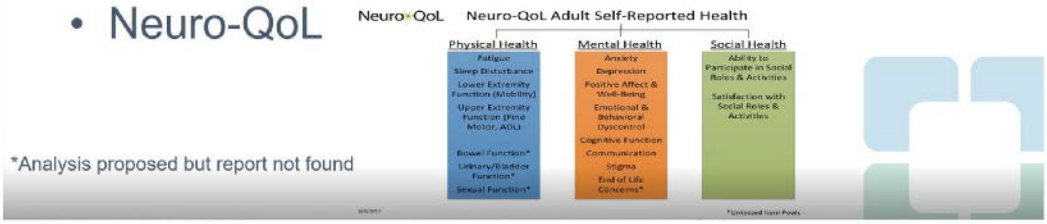
Background: There are potential benefits to stopping DMTs in patients with MS and stable disease/no evidence of disease activity (NEDA), such as reduced monitoring requirements and improved overall sense of wellbeing. Reasons for stopping DMTs include lack of efficacy, poor tolerability and concerns with adherence or persistence. Treatment guidelines on stopping DMTs in MS are not currently evidence based.

ADaptIve Ocrelizumab/Ofatumumab dosing vs. Induction-Maintenance Study (ADIOS-IM Study)
(Giovannoni presentation)



MS-PATHS as a Data Source
(Miller presentation)

- Collaborative of 10 health care institutions in 3 countries
- Functions as a learning health system
- Includes a patient self-administered clinical assessment with automated data collection
- Neuro-QoL



*Analysis proposed but report not found

Biomarkers/Translational Therapy

Scientific Session 11: Global networks in MS

Thursday, 14 October 15:00 – 16:30 CEST

Speakers: Bernhard Hemmer, Bassem Yamout, Victor Fernando Hamuy Diaz de Bedoya, Kazuo Fujihara

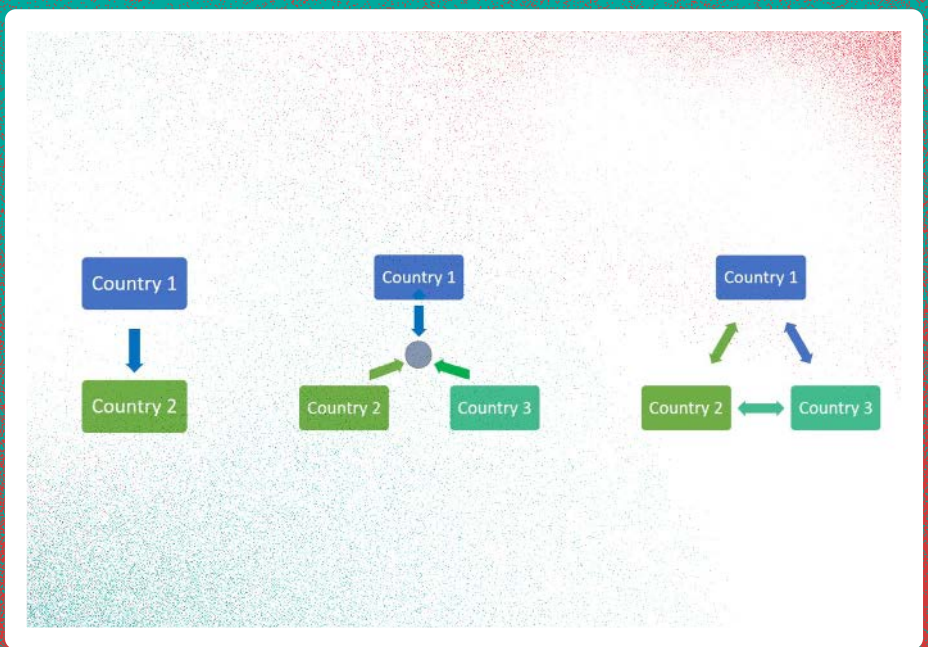
Chairs: Alexey Boyko, Jefferson Becker

Conclusion: Cross-border healthcare collaborations are needed for the advancement of MS knowledge and to improve MS care worldwide. Standardisation in MS benefits patients by reducing hurdles to treatment and research and improving treatment standards. Diagnosis technology, treatment options and public awareness of MS in Latin America have all recently improved, although implementation of cost-effective treatment strategies in the region still presents a challenge. Global networks have produced remarkable results which have led to improvements in the quality of life of people with MS.

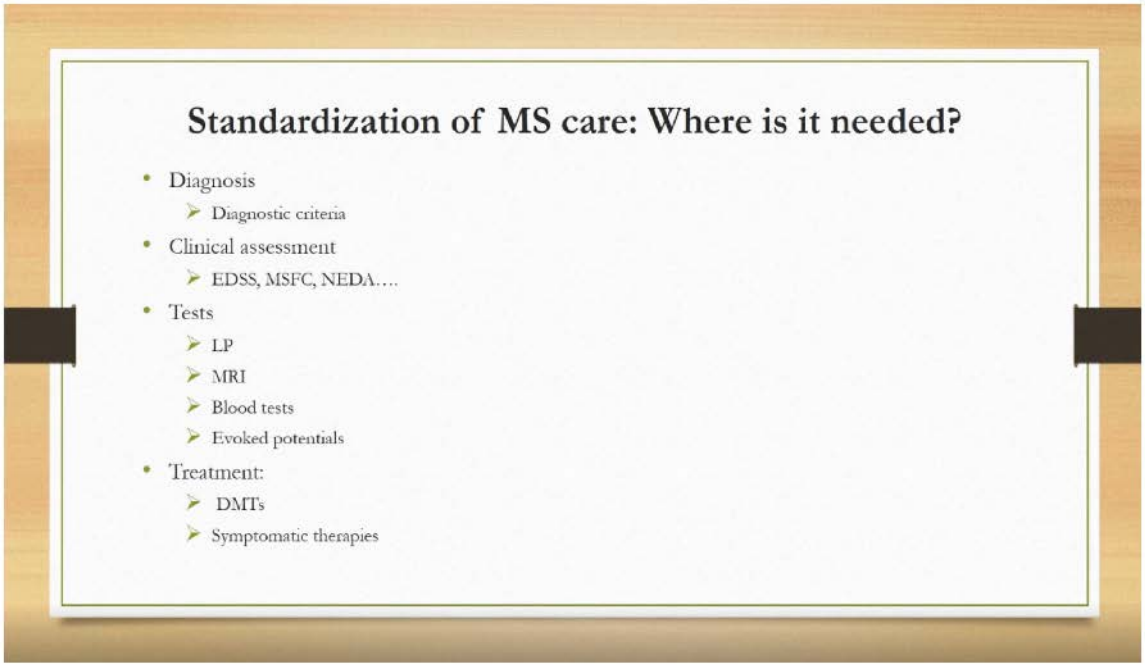
What's New: The EU cross-border healthcare directive provides a minimum set of patient's rights and allows patients access to additional healthcare options abroad, as well as providing a legal basis for European healthcare collaboration. Hurdles to cross-border healthcare collaborations include trust and willingness to collaborate, legal and data/IT issues, healthcare costs, and standardisation of treatments and procedures. Global standardisation in MS is important to ensure positive clinical outcomes, improve safety, lower costs and allow collaborative research. Diagnostic criteria, magnetic resonance imaging use and treatment algorithms are currently standardised whereas testing, clinical assessments and monitoring still require standardisation. International MS treatment recommendations are not followed in parts of Latin America and this is related to costs of diagnosis and treatment. Treatment access can vary within a country due to variations in health insurance coverage, with some insurance policies only covering generics/biosimilars that have not been adequately assessed for safety and efficacy. Furthermore, some poorer countries do not have approved treatments and these therefore need to be used off-label.

Background: Cross-border healthcare collaborations can involve a transfer, movement or exchange of individuals, services and resources. Standardisation in healthcare is the evidence-based selection of healthcare products, services, and treatment approaches including diagnostic techniques and clinical assessments. In Latin America, MS is an epidemiologically emerging disorder and is not yet a priority for public health in the region, and there are disparities in the quality and efficiency of the healthcare provided.

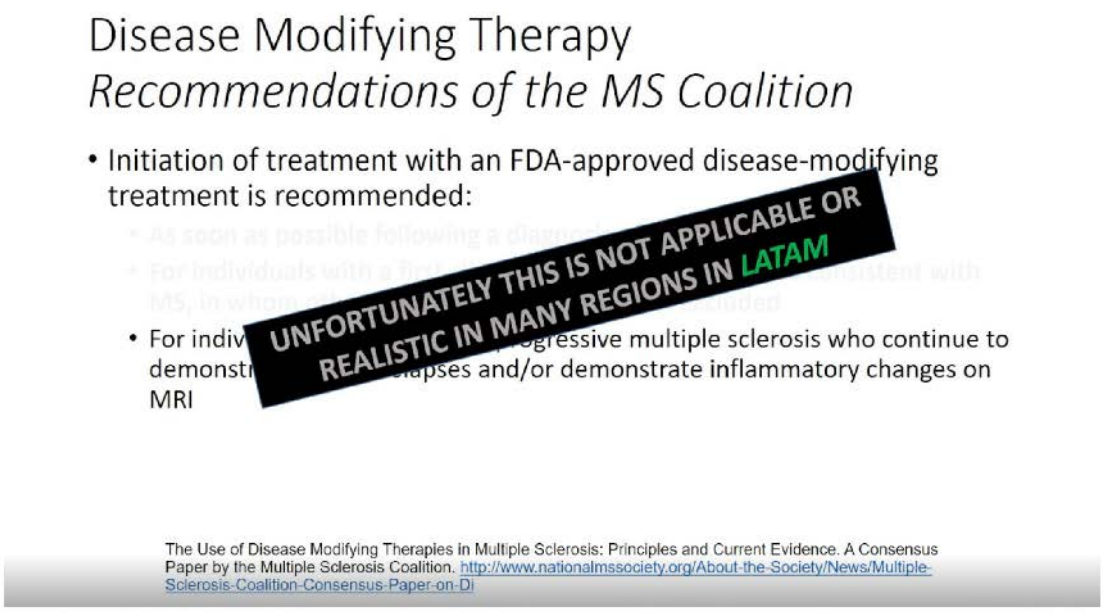
Interaction models for Cross-border Healthcare
(Hemmer presentation)



Standardization of MS care: Where is it needed?
(Yamout presentation)



Disease Modifying Therapy
Recommendations of the MS Coalition
(Hamuy Diaz de Bedoya presentation)



Biomarkers/Translational Therapy

Burning Debate: B-cell depletion therapies (anti-CD20) should be administered indefinitely according to their marketing authorisations as a treatment for multiple sclerosis

Thursday, 14 October 16:45 – 17:45 CEST
Speakers: Fredrik Piehl; Emma Tallantyre
Chairs: Jiwon Oh

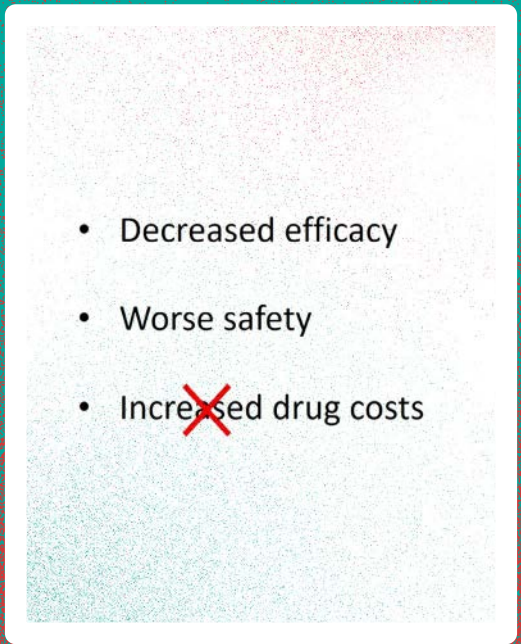
Conclusion: For: Robust evidence for the benefits of extended dosing of anti-CD20 treatments on improved safety and maintained efficacy is still lacking. Until further data become available, the strongest current evidence should be followed which indicates that regular dosing will help to ensure efficacy and prevent disease progression.

Against: Extended dosing of anti-CD20 treatments can reduce the potential cumulative safety risks without impacting efficacy; dosing should therefore be personalised and not indefinite.

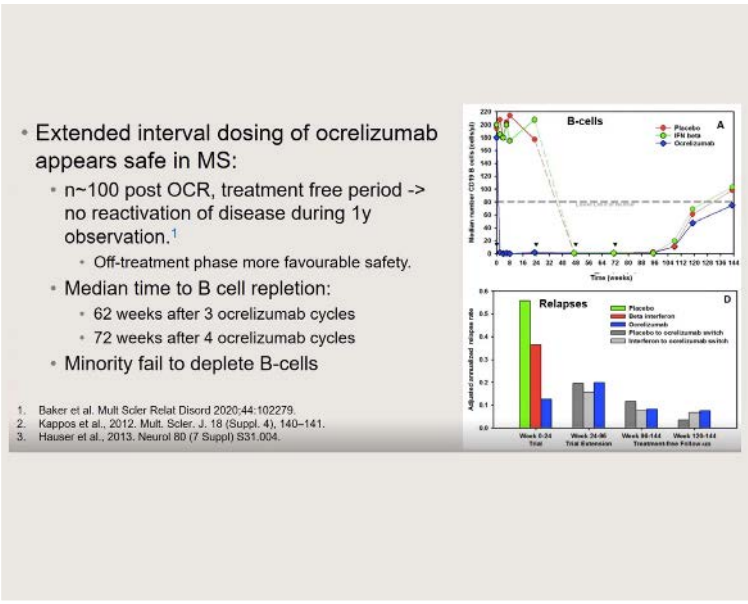
What's New: Personalised dosing may be beneficial for patients receiving anti-CD20 treatments. Recent studies show that anti-CD20 treatments have a durable effect on supressing B-cell levels and therefore continuous treatment may be unnecessary. Extended interval dosing may therefore improve safety by reducing cumulative anti-CD20 exposure without impacting efficacy. However, evidence on extended dosing intervals is limited by short follow-up periods and/or a lack of comparators. Furthermore, benefits on relapses and MRI activity which are the focus of these studies may not directly relate to effect on disability worsening.

Background: Anti-CD20 therapies have been shown to be effective in Phase 3 trials, with relatively good safety profiles. Labels for anti-CD20 therapies such as ocrelizumab indicate dosing should be every 6 months in the long-term. The risk profiles for disease-modifying therapies (DMTs) vary and may be 'front-loaded' or become apparent later on in treatment (cumulative). Long-term follow-up data for anti-CD20 therapies suggest that the risk is cumulative for this treatment class.

Potential perils by deviating from label
(ie. increasing dosing intervals)
(Piehl presentation)



Evidence for personalized dosing
(Tallantyne presentation)



Biomarkers/Translational Therapy

Poster Tour 8 - Therapy / Global views

Thursday, 14 October 18:00 – 18:45 CEST

Speakers: Bart Van Wijmeersch, Bianca Weinstock-Guttman, Nick G Cunniffe, Zoë Yolanthe Germieke Jocelyn van Lierop, Jannis Müller, Izanne Roos

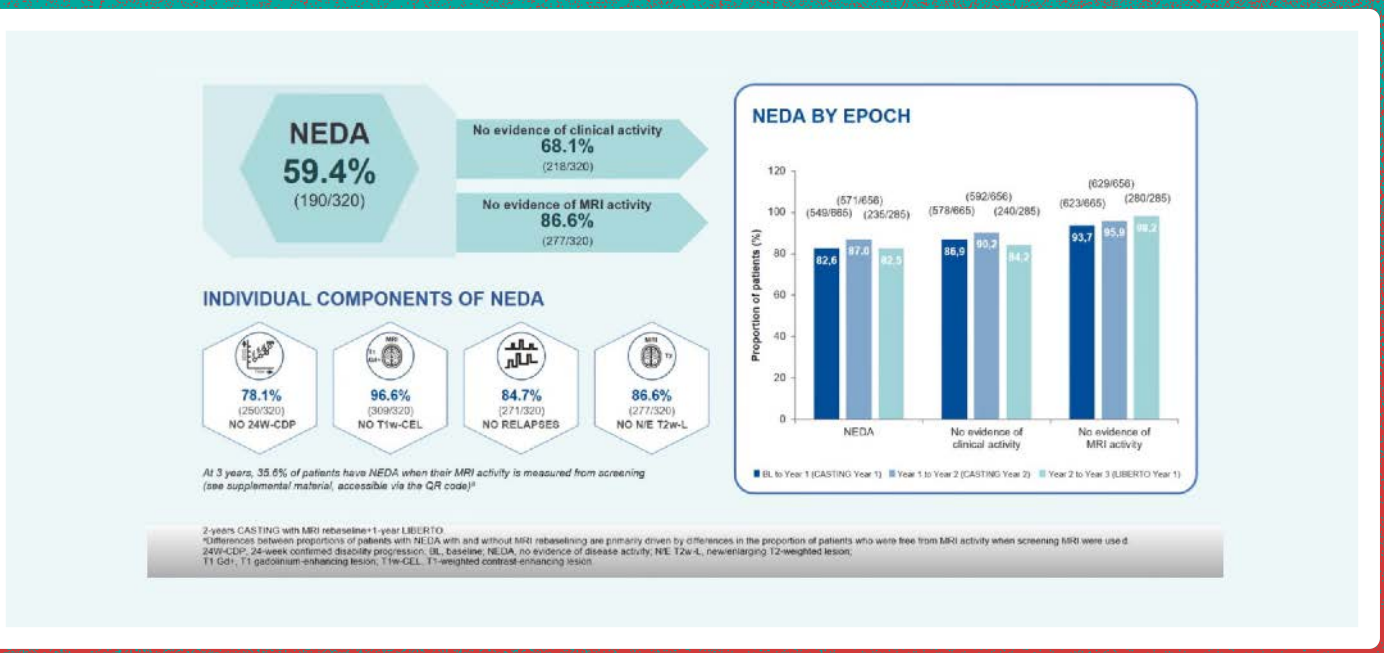
Chairs: Franziska Di Pauli

Conclusion: Treatment with ocrelizumab resulted in consistently low disease activity after 3 years in patients with relapsing remitting MS. Disease activity was low after extended dosing of ocrelizumab due to the COVID-19 pandemic. Real-world findings show patients treated with dimethyl fumarate have more favourable outcomes than those treated with teriflunomide. The real-world risk of disease reactivation following disease-modifying therapy (DMT) cessation varies by DMT; patients previously treated with natalizumab and fingolimod are at the highest risk of disease reactivation and benefit from early introduction of a subsequent DMT. Remyelination drugs may provide long-term benefits for patients with MS.

What's New: Three-year data from the LIBERTO study include 59% patients with no evidence of disease activity (NEDA), 68% with no evidence of clinical activity and 87% with no evidence of magnetic resonance imaging activity. Bexarotene was reported to have a durable effect on full-field visual evoked potentials (VEPs), although tolerability of the drug is very poor. A real-world study found that time to relapse and time to EDSS worsening were both longer in patients treated with dimethyl fumarate versus teriflunomide. The proportion of patients with seroconversion following COVID-19 vaccination was lowest in patients receiving S1PR modulators and B-cell depletion therapies such as ocrelizumab. A study in The Netherlands found that most patients receiving ocrelizumab underwent extended dosing following the start of the COVID-19 pandemic, and short-term disease activity was low during this period. The optimal B-cell level cut-off for extended dosing of ocrelizumab is still unknown, however. Predictors of relapse and disability following treatment cessation were identified in a study of the MSBase and OFSEP registries and included number of relapses in the 12 months prior to cessation. The highest risks versus interferon were found with natalizumab and fingolimod.

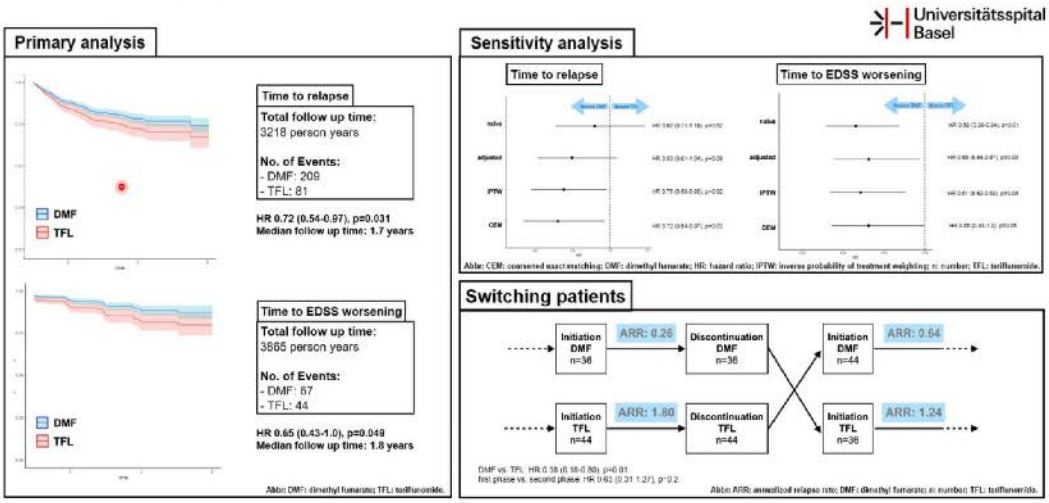
Background: LIBERTO is a long-term extension of the CASTING Phase 3b study which evaluated ocrelizumab in patients with relapsing remitting MS and suboptimal response to other DMTs. A randomised comparative study of the oral DMTs dimethyl fumarate and teriflunomide has not been conducted. Bexarotene is an investigational drug to promote remyelination in relapsing remitting MS. COVID-19 vaccination in patients with MS has resulted in variable antibody responses dependant on which DMTs are used. Extended dosing of ocrelizumab based on B-cell counts has been recommended since the beginning of the COVID-19 pandemic to minimise the risk of COVID-19 infection and reduce the suppression of vaccine response.

Results: 3-years NEDA
(Van Wijmeersch presentation)



Analysis of real-world data showed that in RRMS, dimethyl fumarate treatment was associated with more favorable outcomes compared to teriflunomide

(Muller presentation)



Annualised Relapse Rate: 12 months before baseline (during index treatment) and after treatment cessation

(Roos presentation)