ECTRIMS
EUROPEAN COMMITTEE FOR TREATMENT AND RESEARCH IN MULTIPLE SCLEROSIS

Day 1

ECTRIMS 2021 Congress Reporting

Clinical

Hot Topic 2: COVID-19 and MS

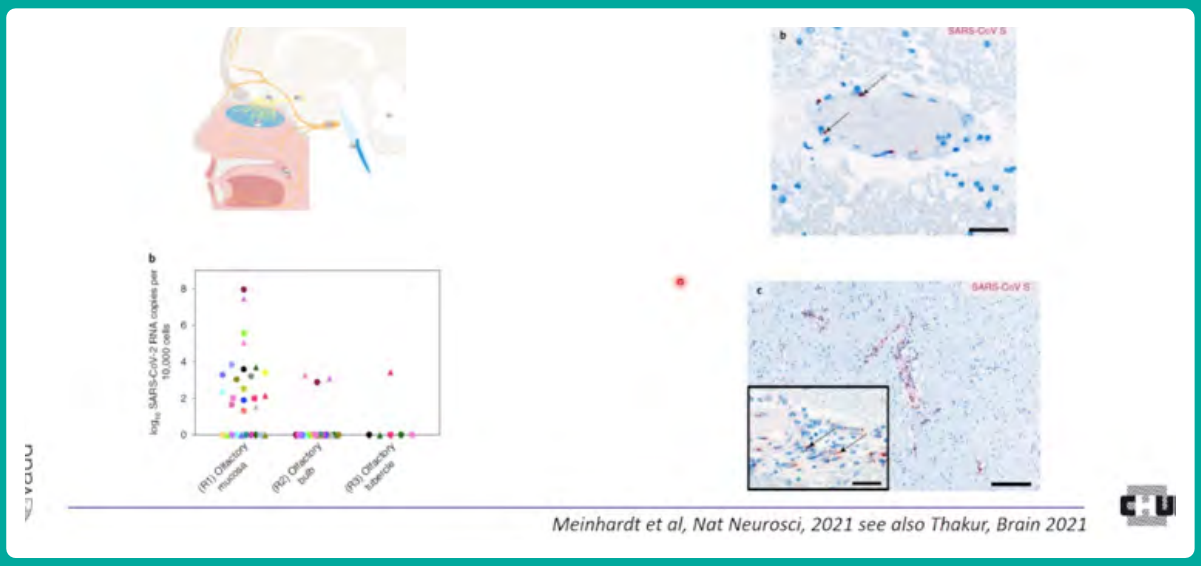
Wednesday, 13 October, 12:00 - 13:00 CEST
Speakers: Renaud Du Pasquier, Maria Pia Sormani, Anat Achiron
Chairs: Andrew Chan, Olaf Stuve

Conclusion: There are limited and primarily indirect data to suggest that the SARS-CoV-2 virus penetrates the central nervous system (CNS), although signs of blood-brain barrier dysfunction have been observed nonetheless, and it is likely that SARS-CoV-2 orchestrates a dysregulated innate immune response. Treatment strategies for MS may correlate with disease severity, with anti-CD20 therapies being associated with more severe COVID-19 infection whilst interferon may play a more protective role, as demonstrated by data derived from several national registries. The effects of treatments on the immune response of patients with MS following vaccination against SARS-CoV-2 should also be considered and an appropriate vaccination strategy applied.

What's New: In situations such as the ongoing global COVID-19 pandemic it is imperative to gain an understanding of the potential effects of infection in higher-risk groups such as individuals with MS. Findings from both immunohistochemistry and polymerase chain reaction experiments have revealed little direct evidence that SARS-CoV-2 can penetrate the CNS; however, some indirect evidence of penetration exists, and several incidences of blood-brain barrier dysfunction have been noted. Analysis of registry data has revealed a correlation between the administration of anti-CD20 therapies such as ocrelizumab and rituximab and more severe COVID-19 infection, with this risk increasing with prolonged treatment. The effects of treatments for MS on the effectiveness of COVID-19 vaccination with the Pfizer SARS-CoV-2 vaccine have also been examined. The timing of vaccination in those receiving certain treatments may be important in ensuring an adequate immune response. Moreover, recommended absolute lymphocyte counts should be achieved before treatment and patients should switch to alternative medications where necessary.

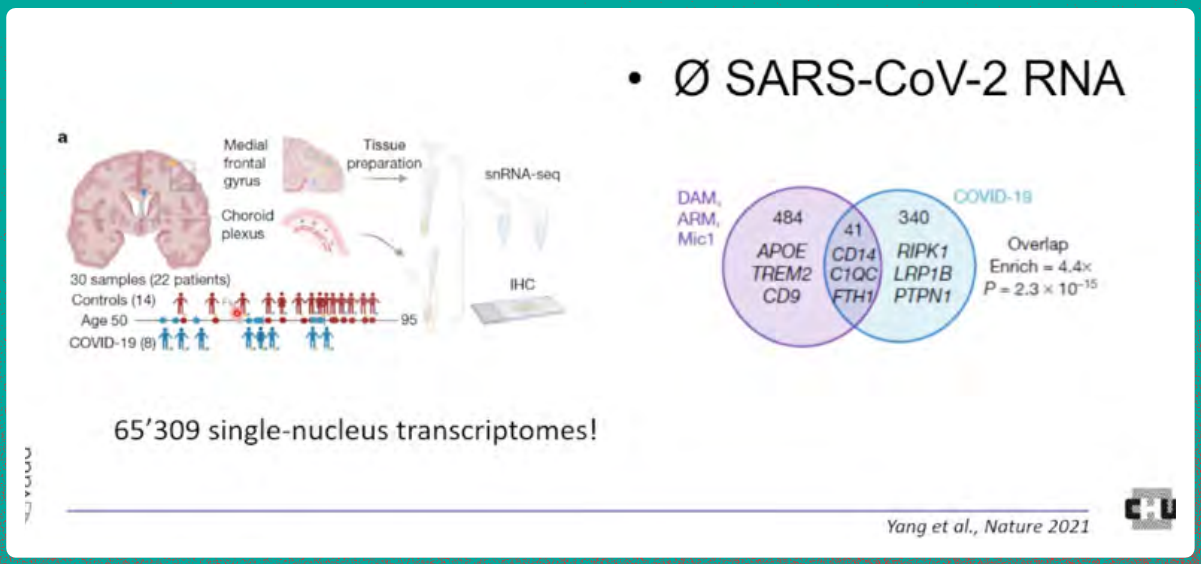
Background: SARS-CoV-2 is a novel virus and the causative agent underlying the COVID-19 pandemic. As COVID-19 is a newly emerging disease, there is a need to identify the potential effects of SARS-CoV-2 beyond respiratory infection and to gain an understanding of any additional risks, including treatment-associated risks, for individuals with conditions such as MS. Registry data and single country studies have limitations, but in times of emergency they provide a good source of information and have the potential to identify common trends among patients.

Possible ways of SARS-CoV-2 entry into the brain
(Du Pasquier presentation)



Meinhardt et al, Nat Neurosci, 2021 see also Thakur, Brain 2021

Dysregulation of brain and choroid plexus cell types in severe COVID-19
(Du Pasquier presentation)



Yang et al., Nature 2021

MuSC-19 Risk factors
(Sormani presentation)

Additional analyses:

Rituximab (n=27)
Ocrelizumab (n=153)

Variable	Multivariate Analysis* OR (95% C.I.)	p
Disease modifying therapy		
No therapy	ref	
Interferon	0.34 (0.15-0.77)	0.009
Other drugs	0.74 (0.48-1.12)	0.15
Ocrelizumab	1.71 (1.02-2.88)	0.04
Rituximab	2.77 (1.10-6.99)	0.03

Anti-CD20 duration

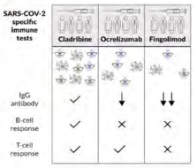
	Ocrelizumab	Rituximab
<6 months	24%	11%
6-12 months	18%	26%
12-24 months	37%	19%
>24 months	21%	44%

Variable	Multivariate Analysis* OR (95% C.I.)	p
No therapy	ref	
Other DMTs	0.68 (0.45-1.04)	0.09
Anti-CD20 <= 6months	1.56 (0.65-3.77)	
Anti-CD20 6months-1 year	1.68 (0.69-4.03)	p<0.001
Anti-CD20 1 year-2 years	1.74 (0.83-3.64)	(trend)
Anti-CD20 >2 years	2.75 (1.28-5.88)	

MS COVID-19 vaccination proposal
(Achiron presentation)

Proposal for MS *COVID-19 vaccination

MS untreated	Cladribine	Ocrelizumab	Fingolimod
No restrictions	At least 4.4 months after last dosing	At leas 8.9 months following last dosing, especially when older than 60 years	Consider switch to a vaccination safe medication
Recommended absolute lymphocyte count >1000 cells/m³			
Follow SARS-COV-IgG response within 3-6 months after vaccination			



*PfizerBNT162b2 m-RNA vaccine

Clinical

Plenary Session 1: Welcome Addresses and ECTRIMS Lecture

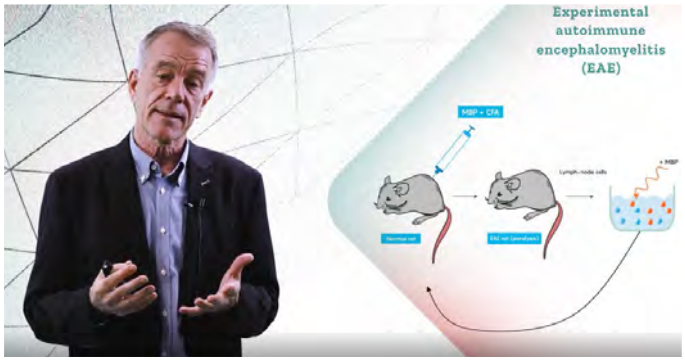
Wednesday, 13 October, 16:15 – 16:45 CEST
Speakers: Roland Martin
Chairs: Maria Pia Amato, Mar Tintoré, Thomas Berger

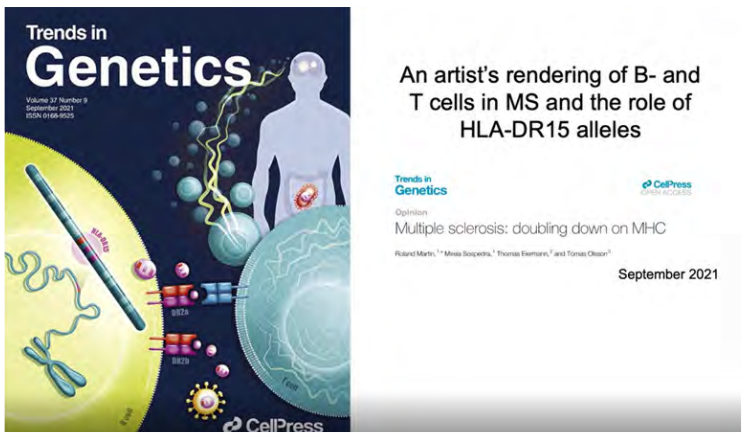
Conclusion: Translational research in MS is a continuing success and will potentially lead to the development of therapies that target B-cell function more specifically, as well as to the development of antigen-specific, neuroprotective and remyelinating therapies.

What's New: Unlike treatments for many other neurological diseases such as Alzheimer's, the development of treatments for MS has been very successful to date, although unmet medical needs clearly remain. In parallel, research about the etiological factors, both genetic and environmental, and also the disease mechanisms of MS have advanced. Studying the mode of action of approved treatments for MS together with autologous hematopoietic stem cell transplantation has enabled translational research to come full circle back to the laboratory. Conversely, basic research has been translated not only into understanding MS, but also into designing new therapies.

Background: In the last century, basic neuroimmunology focused on attempts to reproduce important aspects of MS in animal models. For a considerable time, a viral aetiology was favoured, and several lines of evidence from both virus- and myelin protein-induced animal models, but also the examination of MS brain lesions suggested an (auto-)immune pathogenesis. In the 1990s, the first two treatments, interferon-beta and glatiramer-acetate, became available which were based on the above data. A decade later, the anti-VLA4 antibody natalizumab, which is highly effective in MS, was approved. Natalizumab is probably the best example of successful translation from findings in the animal model, experimental autoimmune encephalomyelitis (EAE), to MS.

(Martin presentation)





Clinical

Poster Tour 1 - Clinical

Wednesday, 13 October, 16:45 – 17:30 CEST

Speakers: Stefanie Binzer, Gavin Giovannoni, Jae-Won Hyun, Maria Cruz Sádaba, Ermelinda De Meo

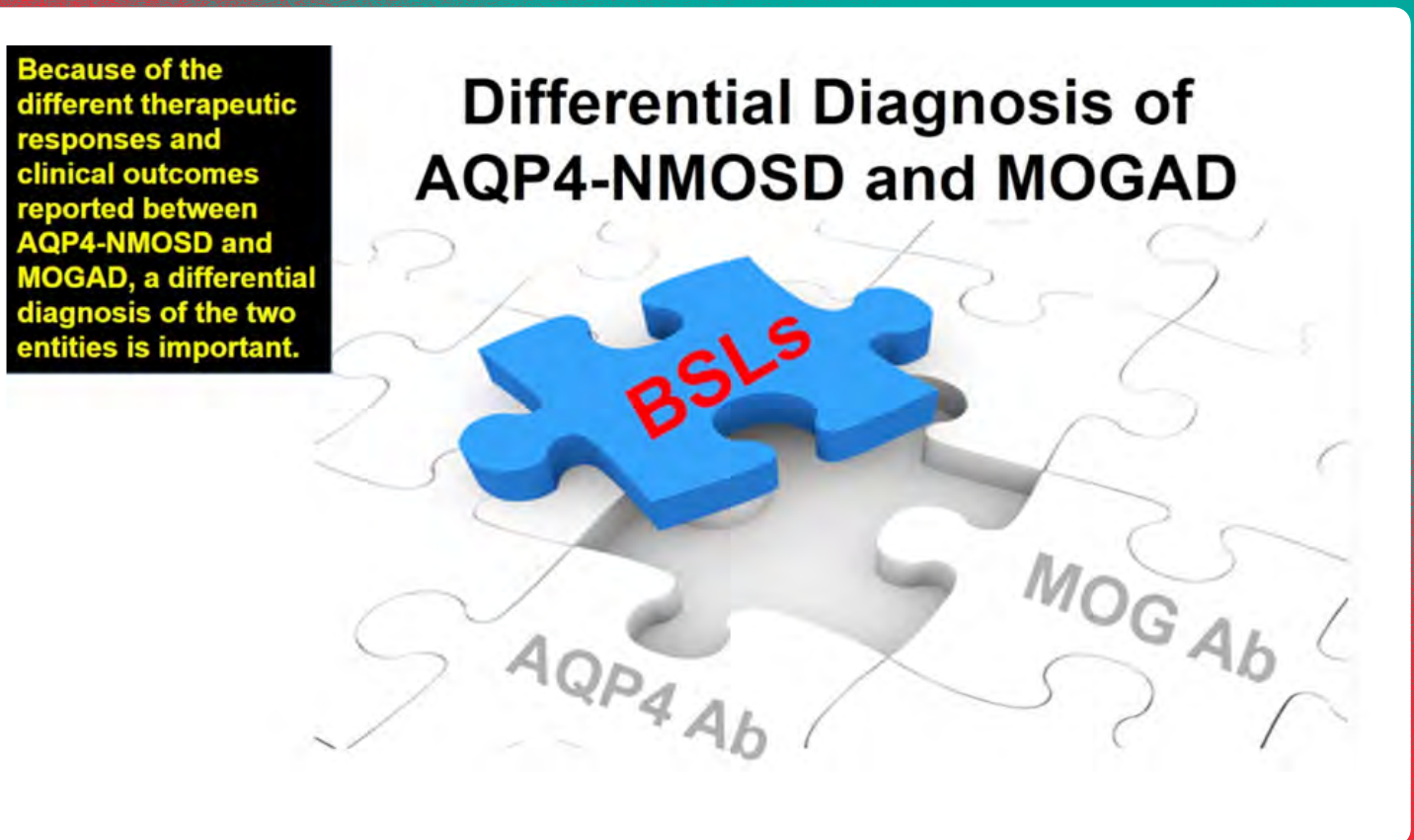
Chairs: Marcin Mycko

Conclusion: Treatment of patients with neurological disorders may be improved by advances that differentiate between patients with aquaporin-4 (AQP4) antibody-positive neuromyelitis optica spectrum disorder (NMOSD) versus those with myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD). The use of magnetic resonance imaging (MRI) activity, rather than relapses, should be incorporated when determining disease activity in patients with secondary progressive MS (SPMS). Paediatric patients with MS who are at risk of treatment failure can be identified by using a simple paediatric MS-specific score combining measures of relapse and MRI activity. Comorbidity management is important in patients with MS.

What's New: A recent study showed that the presence of brighter spotty lesions on spinal MRI T2 imaging can help to differentiate between AQP4 NMOSD versus MOGAD. Other studies in patients with MS have focused on identifying those at risk of disease progression. Using real-world and clinical trial data, MRI activity was shown to be a more sensitive tool for measuring disease activity than relapses in patients with SPMS. The results of an Italian registry study showed that interferon-beta treatment failure and disease progression at 3 years were predicted in paediatric patients with MS using a score based on clinical relapses (<2 versus ≥2) and MRI activity (<3 versus ≥3 new T2 or Gd+ lesions) at 1 year. In addition, the presence of concomitant autoimmunity (Crohn's disease, ulcerative colitis, type 1 diabetes) and other comorbidities were associated with worsened MS disability in a Swedish registry study.

Background: Optimal management of patients can vary depending on differential diagnosis, disease stage or the presence of comorbidities. It is therefore important to correctly identify these characteristics in patients with neurological disorders to help optimise treatment.

(Hyun presentation)

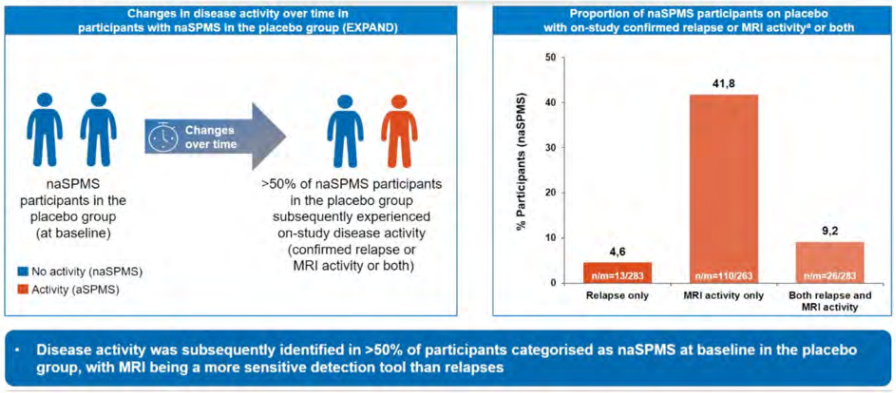


(Giovannoni presentation)

Giovannoni et al. | P001

MRI Activity is a More Sensitive Tool to Measure Disease Activity Than Relapses In the Clinical Trial Setting

EXPAND (Core Part)

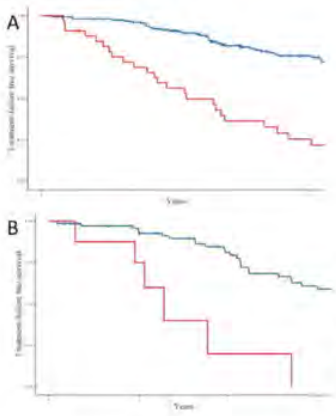


- Disease activity was subsequently identified in >50% of participants categorised as naSPMS at baseline in the placebo group, with MRI being a more sensitive detection tool than relapses

(De Meo presentation)

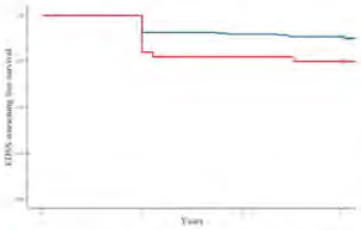
Results and conclusions

Treatment failure free survival in training set (A) and validation set (B)



PPV = 75%
NPV = 73%
Sensitivity = 44%
Specificity = 91%
Accuracy = 68%.

EDSS-worsening free survival



PPV = 20%
NPV = 85%
Sensitivity = 18%
Specificity = 88%
Accuracy = 53%

- The combination of clinical relapses with substantial MRI activity appeared as the best predictor of short-term treatment failure and disease progression in pediatric MS patients.
- The adoption of this simple and pediatric MS-specific score in the clinical practice could help clinician in optimizing treatment strategies.

(Binzer presentation)

Out of 8,972 MS patients:

→ 88 (1.0%) had T1D,

→ 78 (0.9%) had UC,

→ 77 (0.9%) had CD

	Hazard ratio (95% CI)					
	EDSS 3		EDSS 4		EDSS 6	
Comorbidity	EDSS 3	Charlson's comorbidity ≥1	EDSS 4	Charlson's comorbidity ≥1	EDSS 6	Charlson's comorbidity ≥1
T1DM	1.53 (0.80-2.91)		2.37 (1.09 -5.15)		1.98 (0.73-5.32)	
CD	1.87 (C1.09-3.20)	1.53 (1.19-1.96)	1.06 (0.51-2.21)	1.95 (1.42-2.69)	1.24 (0.45-3.361)	2.76 (1.77-4.32)
UC	1.30 (0.70-2.43)	1.55 (1.21-4.99)	0.47 (0.19-1.174)	2.03 (1.47-2.80)	2.47 (0.99-6.14)	2.75 (1.76-4.28)
IBD	1.82 (1.19-2.79)		1.37 (0.92-2.04)		2.00 (0.95-4.22)	

Crohn's disease (CD), Ulcerative colitis (UC) or type 1 diabetes (T1D), inflammatory bowel disease (IBD)

Clinical

Scientific Session 1: NMO spectrum and MOG antibody associated disorders: distinctions and overlaps

Wednesday, 13th October, 13:15-14:45 CEST

Speakers: Romana Höftberger, Dean M Wingerchuk, Laura Cacciaguerra, Valentina Camera, Sara Carta, Hannah Zhao-Fleming

Chairs: Jacqueline Palace, Friedemann Paul

Conclusion: Similar demographic and clinical features exist between patients with neuromyelitis optical spectrum disorder (NMOSD) and NMOSD-like conditions. The occurrence of new remission silent lesions is rare in demyelinating diseases; however, such lesions may be associated with imminent relapses in both anti-aquaporin-4 antibody (AQP4)-positive NMOSD and myelin oligodendrocyte glycoprotein (MOG) antibody disease (MOGAD). Further research is required to elucidate the relevance of MOG antibodies detected in a high proportion of MOGAD patients, in particular those with myelitis-like clinical features. Patients with AQP4-positive NMOSD are more likely to require a longer period of ventilatory support during an acute attack of myelitis when compared with patients with MOGAD who typically require ventilation following acute attacks of encephalitis.

What's New: Examination of differences between patients with NMOSD and NMOSD-like conditions revealed similar demographic and clinical features in most conditions, with the exception of lower disability in those patients with recurrent optic neuritis and lower levels of diffuse cortical atrophy in those with recurrent myelitis. Application of a clustering analysis identified three groups of patients that might mirror different prognosis between diagnoses. MOG antibodies are present in a high proportion of MOGAD patients with the presence of MOG antibodies in the CSF associated with a greater degree of disability. Assessment of the frequency of new remission silent lesions detected by magnetic resonance imaging, and their association with relapse in patients with AQP4-positive NMOSD and MOGAD demonstrated that such lesions occur infrequently but may be associated with imminent relapse. Acute attacks requiring ventilatory support occur more frequently in patients with AQP4-positive NMOSD compared with MOGAD patients, are more severe, more likely to need treatment with plasmapheresis, and require longer periods of ventilation.

Background: AQP4 and MOG antibodies are associated with demyelinating diseases, with AQP4 antibodies targeting astrocytes and MOG antibodies myelin. NMOSD and MOGAD cause inflammation in the nervous system, and clinically, NMOSD, MOGAD and MS can appear similar. However, despite their overlapping clinical and radiological features, the epidemiology, characteristics, and treatment of these disorders can differ. Currently, there are no consensus diagnostic criteria for MOGAD.

(Cacciaguerra presentation)

Results / Unsupervised clustering

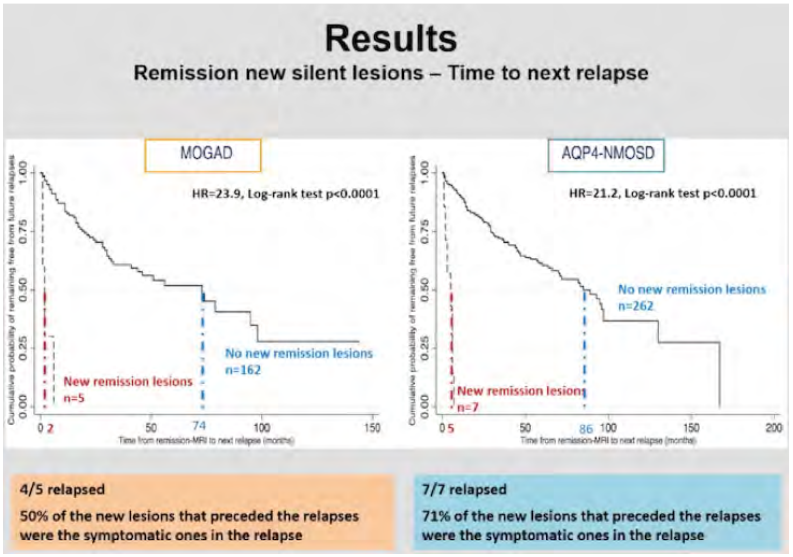
Clustering analysis based on structural measures identified three groups of NMOSD/NMOSD-like patients, with **similar ON and cord volume, ON lesions length, number of optic neuritis/myelitis and phenotypes**

Variable	Cluster #1	Cluster #2	Cluster #3	p
Age [years]	**50.4 (12)**	38 (12)	40 (12)	0.004
EDSS (range)	5.0 (1-9)	4.0 (1-8.5)	**3.5 (0-8)**	0.021
% OCBs[a]	16.7	0.0	**39.5**	0.037
Optic nerve volume [mm^3]	117 (4.3)	**111 (6.0)**	119 (3.7)	0.048
nCSA [mm^2]	105.6 (4.4)	**88.7 (6.6)**	101.55 (3.8)	0.041
T2LV [ml]	**2.7 (4.9)**	1.1 (2.3)	2.5 (6.7)	0.048
Cortical thickness [mm]	2.30 (0.1)	2.31 (0.2)	**2.22 (0.1)**	0.002

Unless otherwise specified, results refer to ANOVA; [a]Fisher's exact test

- #1 (34%): Older and higher brain T2 lesion volume
- #2 (13%): Optic nerve and spinal cord atrophy
- #3 (53%): Lower EDSS and more cortical atrophy

(Cacciaguerra presentation)



(Carta presentation)

RELAPSES

- **Mean follow up**: 40.99 SD 55.89, MOGs-c+ 25.84 (p 0.0001)
- **ARR**: mean 0.46/year SD±1.23. Adults 0.56 SD±1.16 , Pediatrics 0.37±SD 1.29
- **No relevant differences between groups**

EDSS at FU	Overall	MOGs+c-	MOGs+c+	MOGs-c+	
all cohort (mean)	1.52 SD±2.21 (n=250)	1.41 SD±2.24 (n=74)	1.28 SD±1.23 (n=144)	2.84 SD±2.87 (n=32)	p=0.0016
Adults (mean)	2.31 SD±2.51 (n=123)	1.97 SD±2.46 (n=40)	2.20 SD±2.23 (n=57)	3,11±SD 3.03 (n=27)	p=0.2274
Pediatrics (mean)	0.76 SD±1.53 (n=127)	0.79 SD±1.81 (n=34)	0.71 SD±1.44 (n=88)	1.4 SD±1.14 (n=5)	p=0.1010

(Zhao-Fleming presentation)

Attack and ventilatory details	**MOGAD (n=8)**	**AQP4+NMOSD (n=11)**	***p*-value**
Episode represented 1st attack	7/8 (87.5%)	2/11 (18%)	**0.006**
Median EDSS just prior to attack	0 (0-3.5)	4 (0-8)	**0.02**
Encephalitis/rhombencephalitis	8/8 (100%)	2/11 (18%)	**<0.001**
Myelitis/Quadriparesis	2/8 (25%)	11/11 (100%)	**0.001**
Median (range) duration of respiratory support in days	2 (1-7)	19 (6-330)	**0.01**
Tracheostomy required	1/8 (13%)	5/11 (45%)	0.18

Pathogenesis

European Charcot Foundation Symposium: The mystery solved project - an MS initiative of the ECF to foster research on human brain tissue

Wednesday, 13 October, 12:00 – 13:00 CEST

Speakers: Patrick Vanderdonckt, Claudia Lucchinetti, Richard Reynolds, Hans Lassmann

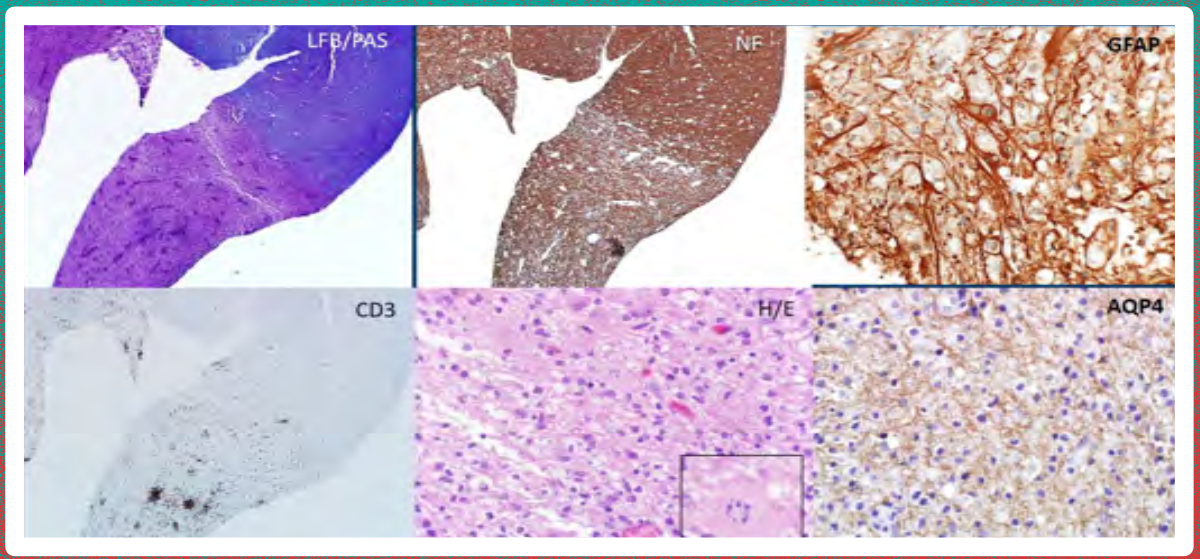
Chairs: Maria Pia Amato, Giancarlo Comi

Conclusion: Brain biopsy provides the opportunity for detailed clinical-radiographic-pathologic correlation in MS and provides insights into the earliest events in disease pathogenesis. In the omics era, technology continues to evolve and there is a great opportunity to consider the use of brain tissue for future application in detailed and rigorous omics profiling. Much MS research relies on the availability of post-mortem MS tissues so collection of human brain samples, gathering of biopsy data and augmentation of existing brain banks is important to further this vital research into MS causes and treatments.

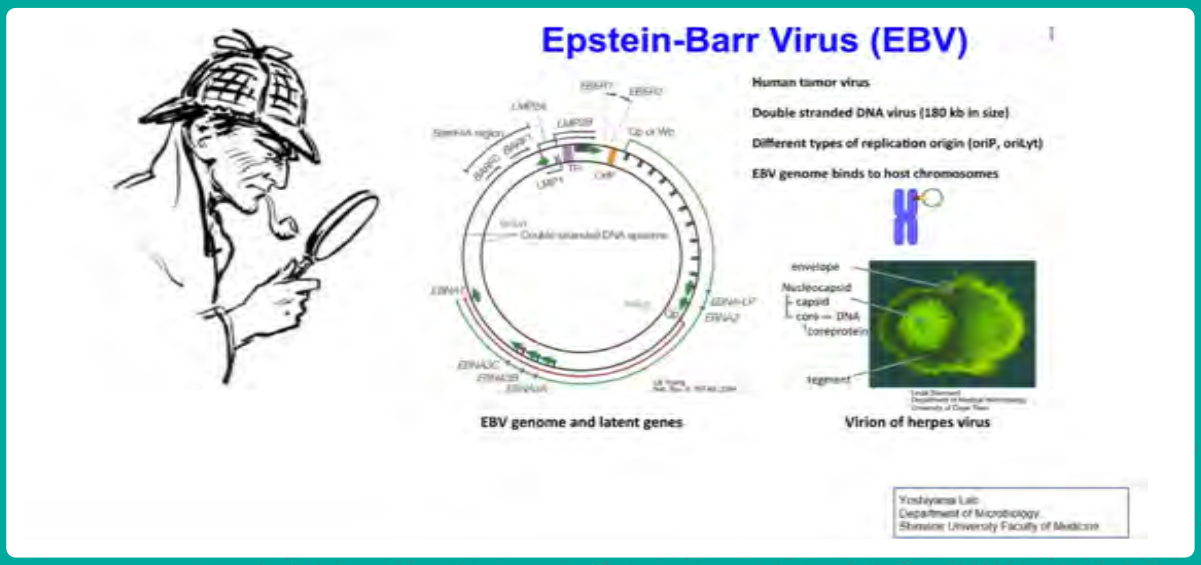
What's New: The Mystery Solved project has been conceived to support research into the cause of MS, focusing specifically on the role of Epstein Barr Virus (the prime suspect!). It will create an international network of MS experts alerted to collect rare biopsy and autopsy materials from active MS patients. Mystery Solved aims to address the lack of active MS tissue currently available for research and to apply advances in research technology including multi-omics and new genetic/virological techniques. A position paper on the Mystery Solved project is currently in development summarising the current state and suggestions for improvement in tissue donations for MS research. In testament to the importance of post-mortem MS tissues, several recent studies have used brain bank material to carry out cutting-edge research into immune cell isolation, proteomics, small nuclear RNA (snRNA) sequencing, single nucleotide polymorphisms (SNPs) and auto-antigen analysis, together with new animal models.

Background: Brain biopsy is a rare event in the diagnostic workup of MS but can be critical to secure an accurate diagnosis. Before carrying out a brain biopsy, it is vital to first check aquaporin-4 (AQP4) and myelin oligodendrocyte glycoprotein (MOG) antibodies and perform imaging of the entire neuroaxis. Strong diagnostic neuropathological expertise is essential to support interpretation of biopsy findings which can mimic tumour pathology. Brain banks make an important contribution to MS research by providing well preserved human brain tissue for molecular sample, imaging and immunofluorescence.

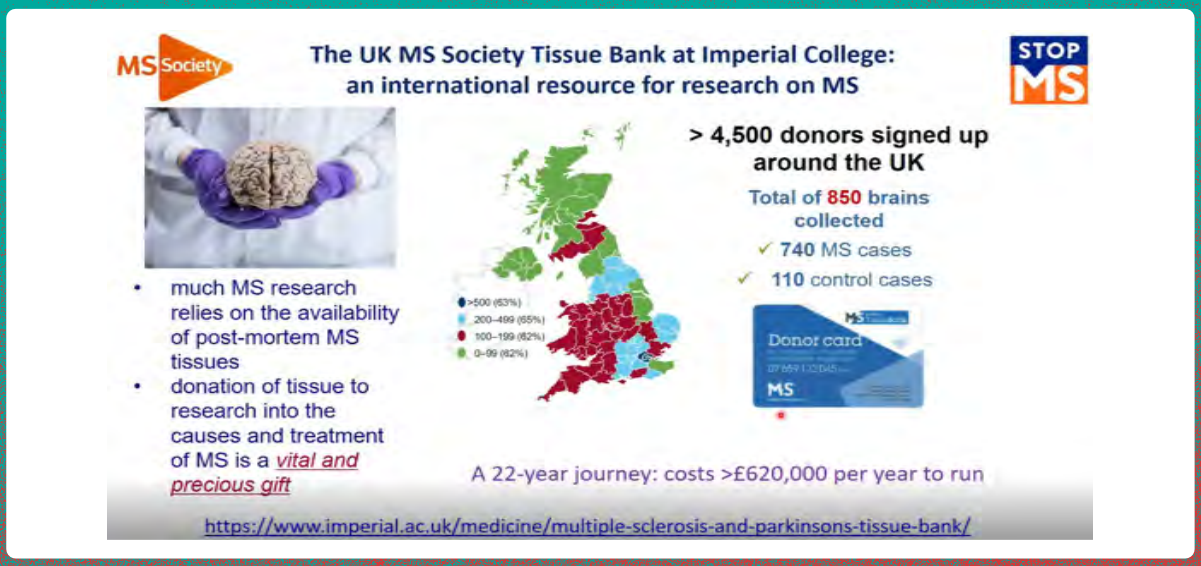
(Lucchinetti presentation)



Mystery Solved Project
(Vanderdonckt presentation)



(Reynolds presentation)



Pathogenesis

Poster Tour 2 - Pathogenesis

Wednesday, 13 October, 16:45 – 17:30 CEST

Speakers: Kristen Hawkins, Nina Louise Fransen, Darius Häusler, Samia Khoury, Tomas Olsson, Pietro Iaffaldano

Chairs: Sonja Hochmeister

Conclusion: Cutting-edge research sheds new light on MS pathogenesis. Reductions in oxysterols are apparent in damaged MS brain. The increased susceptibility of males to develop leukocortical MS lesions may be related to changes in allopregnanolone and 3alphaDIOL in cortical grey matter. Further, translational work exploring the role of B-cells has revealed a direct interaction with the microglia. As regards Epstein Barr virus (EBV) involvement, whether EBV+ exosomes initiate the immune activation during relapse or are a consequence of activation remains to be elucidated. Importantly, many lifestyle and environmental factors interact with MS genes and impact on the risk of relapsing- and progressive-onset MS.

What's New: Research in the human MS brain has shown that low abundant cholesterol and 24S-hydroxycholesterol were reduced in areas of damage, including chronic white matter lesion edges and centres, as were 26-hydroxycholesterol and 7α,26-dihydroxycholesterol. Metabolism of 24S-hydroxycholesterol, essential for brain development and synaptogenesis, was altered.

In MS cortical grey matter, allopregnanolone and induction of 3alphaDIOL (both of which can attenuate neuronal excitotoxicity and inhibit cytotoxic CD8 T-cell responses) were normal-appearing in female but not male patients, in whom CD8 and interferon gamma expression were also increased.

B-cell-derived IL-10 was shown to dampen microglial activation and production of pro-inflammatory cytokines. Depletion of naïve B-cells or B-cell-derived IL10 worsened clinical severity of experimental encephalomyelitis (EAE) and increased the number of CNS-infiltrating immune cells, which in turn was associated with an enhanced expression of molecules involved in antigen-presentation on microglia.

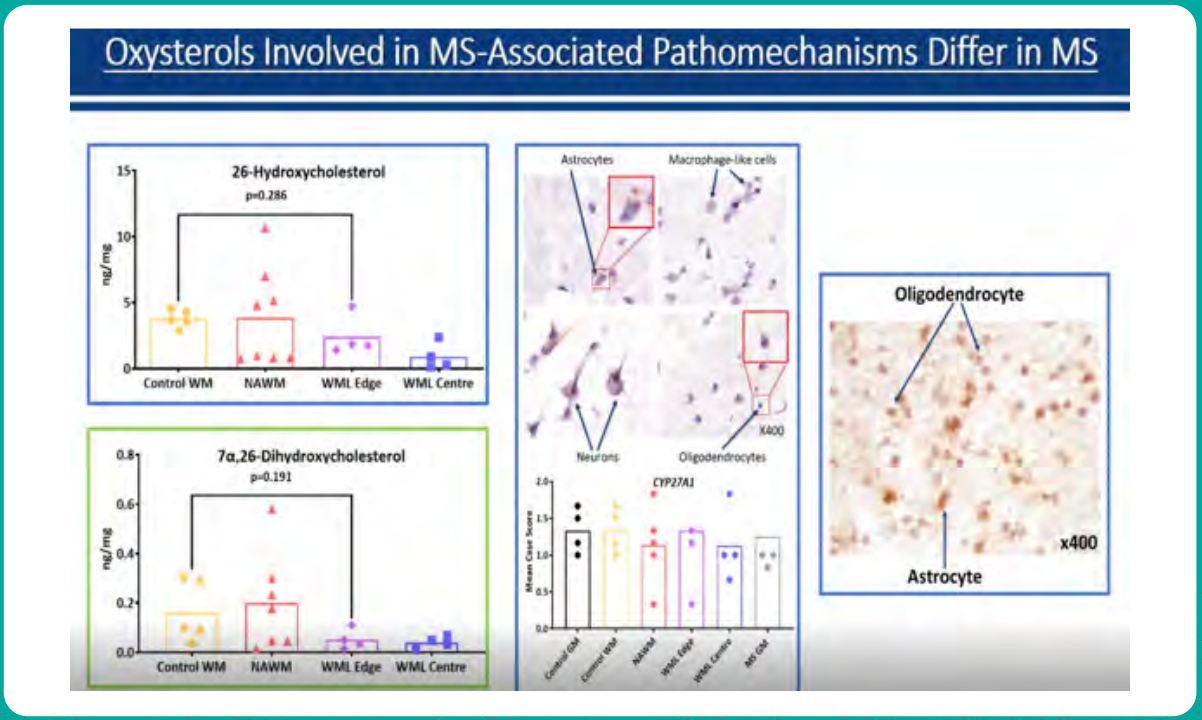
A study of 45 serum-derived exosome preparations isolated from MS patients and healthy controls showed expression of EBV-derived proteins and activated monocyte-derived macrophages in the MS samples - specifically in patients with active disease.

Analysis of available data has confirmed that many similar genetic, lifestyle and environmental factors impact on the risk of relapsing- and progressive-onset MS - all interconnected via their action on the immune system. The majority have modest influences (odds ratios [ORs] ~1.5–2), though influence of most is higher than with non-HLA genes (ORs ~1.1–1.2). Factors exerting their effects during adolescence and early adulthood include EBV, obesity, brain concussion and disturbed diurnal rhythm.

Results from a case-controlled study into COVID-19 in MS using data from the Italian MS Register (IMSR) showed that MS patients at higher COVID-19 risk were typically younger, more frequently women and had coexisting comorbidities. A longer-lasting escalation approach and hospital-based therapies significantly increased the risk of SARS-CoV2 infection.

Background: Research into disease pathogenesis in MS is a key to deepening current understanding of the pathobiological pathways that underpin disease including the role of EBV and B-cell microglia interactions. It is also important in driving greater understanding of genetic, lifestyle and environmental risk factors for MS development and understanding the potential impact of gender on disease evolution.

(Hawkins presentation)



Factors affecting the risk of relapsing and progressive-onset MS
(Olsson presentation)

Lifestyle/environmental factor	Relapsing-onset MS	Progressive-onset MS
	OR (95% CI)	OR (95% CI)
Smoking	1.6 (1.5-1.7)	1.9 (1.6-2.3)
Adolescent obesity	1.7 (1.4-2.0)	1.8 (1.0-3.2)
High EBNA-1 IgG levels	3.0 (2.7-3.3)	2.0 (1.6-2.5)
Low sun exposure	1.3 (1.2-1.4)	1.3 (1.1-1.6)
Snuff use	0.7 (0.6-0.9)	0.6 (0.4-0.9)
Alcohol consumption	0.8 (0.7-0.9)	0.5 (0.4-0.7)

Pathogenesis

Scientific Session 2: Blood-brain-barrier

Wednesday, 13 October, 13:15 – 14:45 CEST

Speakers: Alexandre Prat, Britta Engelhardt, Florian Ruiz, Hideaki Nishihara, Marion Mandon, Maria Højberg Knudsen

Chairs: Inge Huitinga, Hans Lassman

Conclusion: Specific subsets of immune cells express selected cellular adhesion molecules (CAMS) which are key drivers of the migration of B- and T-cells across the blood brain barrier (BBB). It is possible that targeting selected CAMS will affect different phases of MS disease - from relapses to progression - without inducing complete immunosuppression of the central nervous system (CNS). Ongoing research continues to explore other exciting new avenues for potential targeting of the BBB in MS treatment.

What's New: Recent research has shown that endothelial cell-derived oxysterols promote neuroinflammation through suppression of myeloid-derived suppressor cells. Specifically, the expression of Ch25h by CNS endothelial cells promotes the inflammatory imbalance seen in MS. This highlights a potential role for Ch25h inhibitors to promote the expansion of anti-inflammatory/regulatory cells and dampen down pro-inflammatory CD4 T-cells.

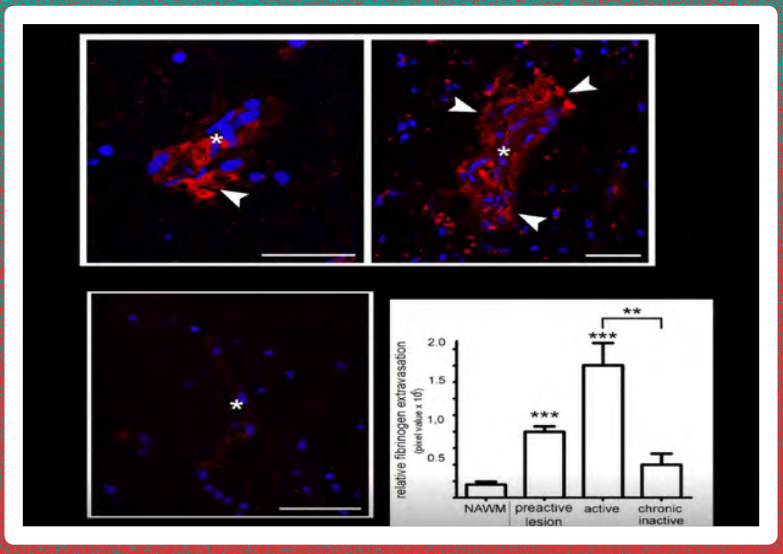
Human induced pluripotent stem cell (hiPSC) modelling of the BBB has identified intrinsic barrier dysfunction in MS patients. Ongoing transcriptome profiling of EECM-BMEC-like cells by RNAseq may help to identify key BBB dysfunction signature genes in MS. These MS patient hiPSC-derived models of the BBB offer the unprecedented opportunity to identify molecular mechanisms mediating BBB dysfunction and could also serve as tools for developing therapeutic strategies for BBB stabilisation.

Emerging evidence suggests that activated Th1 cells infiltrate the cerebrospinal fluid early in relapsing/remitting MS. An infiltration of Tfh1 was seen in the CNS of MS patients, accompanied by expression of key genes such as Prf1. Further analysis is needed to decipher which cells have a pathogenic role in secondary progressive MS and establish whether they are similar to resident memory T-cells.

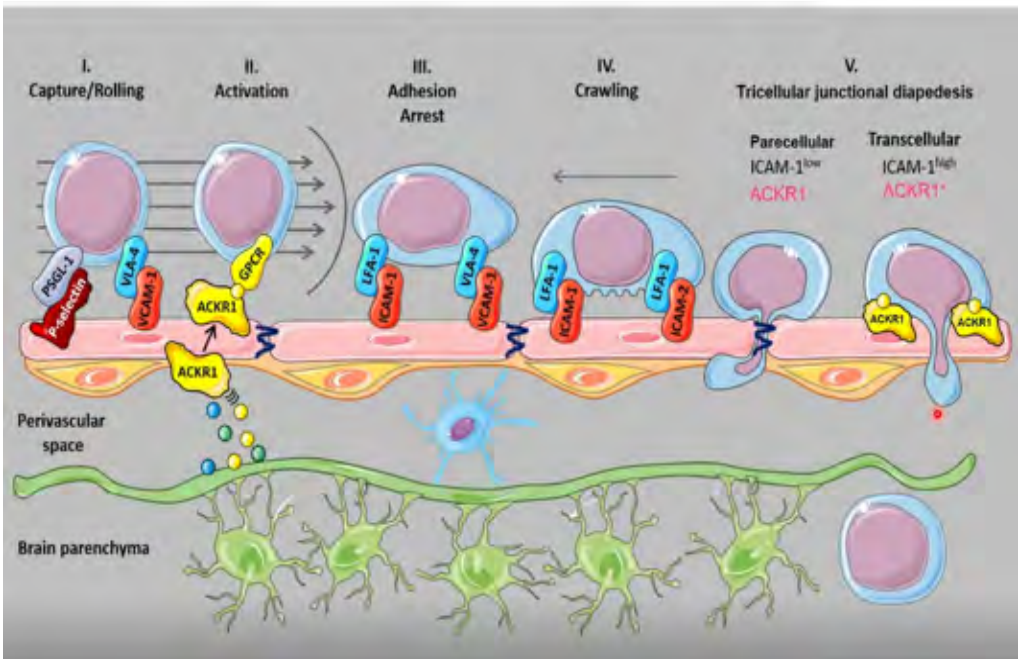
A recent imaging study exploring changes in BBB permeability during alemtuzumab treatment showed that permeability was predictive of outcomes at 2 years [no evidence of disease activity 3 (NEDA-3) maintained versus lost]. BBB permeability from dynamic contrast-enhanced (DCE) MRI could be used to identify patients at risk of disease activity and in need of more intensive surveillance.

Background: The BBB actively controls immune cell trafficking into the CNS and its permeability has been correlated with adverse outcomes in MS. BBB permeability may also act as a potential marker of subclinical disease activity in MS. Adhesion molecules such as ICAM and VCAM-1 play a key role in directing diapedesis and controlling the migration of immune cells across the BBB in MS. More recent evidence also indicates a role for activated leukocyte adhesion molecule (ALCAM) and ARCK1 in promoting the migration of B- and T-cells, respectively across the BBB.

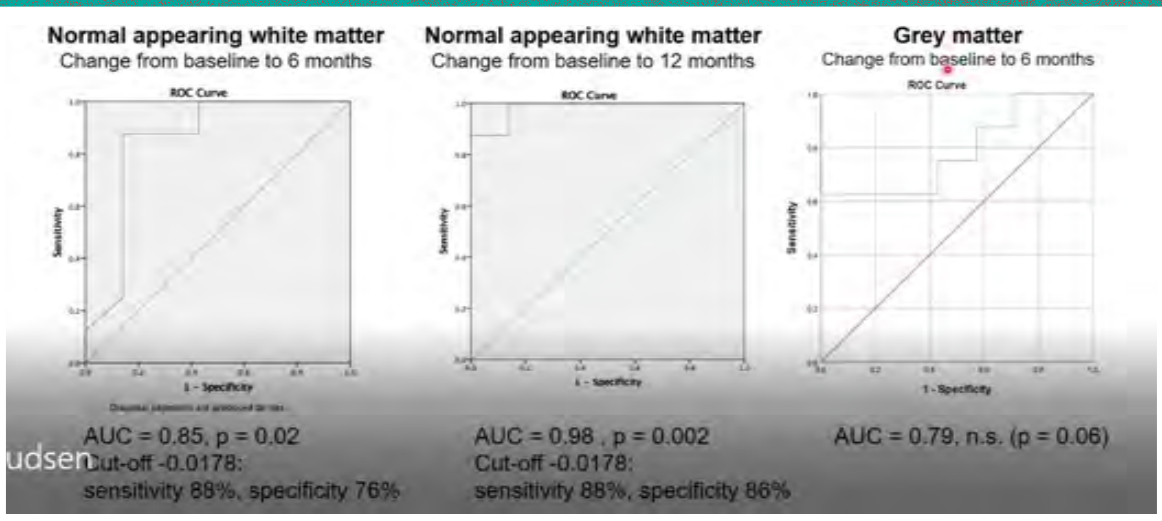
(Prat presentation)



(Engelhardt presentation)



(Knudsen presentation)



Imaging & Non-Imaging

Hot Topic 3: Imaging pathology in MS

Wednesday, 13 October, 12:00 – 13:00 CEST

Speakers: Daniel S. Reich, Nikos Evangelou, Assunta Dal-Bianco

Chairs: Christian Enzinger, Kejal Kantarci

Conclusion: The relevance of the dural lymphatic system and the glymphatic pathway in MS remains uncertain. Studies are ongoing to determine the diagnostic value of the central vein sign in MS. Iron rim lesions (IRL) could be a promising tool for predicting disease progression and monitoring treatment in patients with progressive MS. As changes to IRL are very slow, long-term studies are essential to capture the long-term insights. These are exciting developments, and clear consensus guidelines on the use of the central vein sign and IRL in diagnosing MS are needed.

What's New: Two large diagnostic studies using the central venous sign are ongoing in the US and UK: 1) DiagnoseE using the Central veIn SIgn (DECISIve). A prospective diagnostic superiority study comparing T2* magnetic resonance imaging (MRI) and lumbar puncture in patients presenting with possible MS; and 2) Central vein sign: A diagnostic biomarker in MS (CAVS-MS) study.

Long-term insights of IRL include: slow expansion of IRL and shrinkage compared with non-IRL; IRL are more destructive than non-IRL; iron rims gradually decline over time; IRL are associated with significantly worse cognitive and physical performance.

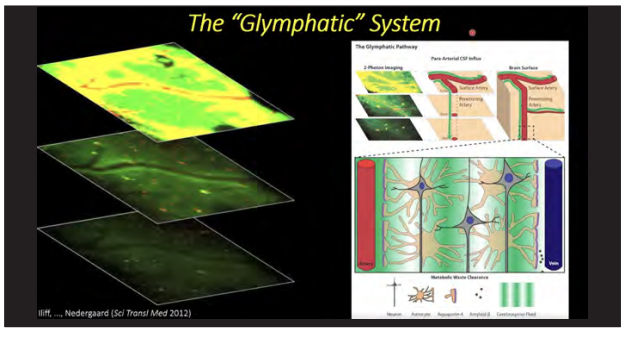
Background: MS involves profound meningeal inflammation of the brain, both early and throughout the disease course, which likely contributes to disease progression. However, optimal imaging methods remain elusive, misdiagnosis of MS is common, and there is a tension between the benefits of early diagnosis and the risk of misdiagnosis.

Leptomeningeal enhancement has been associated with in vivo cortical lesions in MS but better imaging methods are required. The anatomical and homeostatic functional connection to the brain of the dural lymphatic vessels can be visualised by MRI. Also, the glymphatic pathway, which involves the paravascular and interstitial transport of fluid and solids in the brain, can be detected by MRI of intrathecal gadolinium accumulation.

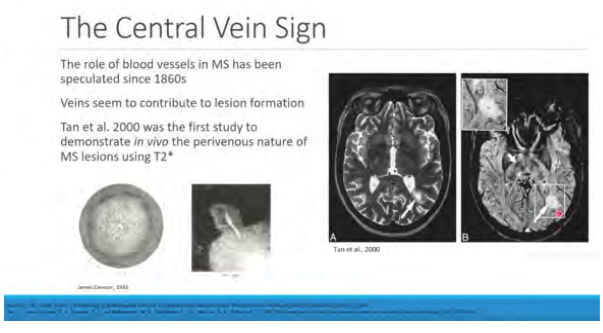
Venous abnormalities related to the development of lesions in MS are widely recognised. The central vein sign has been proposed as a specific biomarker for diagnosing MS, based mainly on findings from ultrahigh-field MRI studies.

Subsets of MS lesions are surrounded by an iron rim in MRI (7T, 3T) and indicate chronic activity. Extrinsic factors are suggested to impair oligodendroglial differentiation and limit repair mechanisms by blocking remyelination in the early phase of inflammation.

(DS Reich presentation)



(Evangelou presentation)



(Dal-Bianco presentation)

Imaging & Non-Imaging

Scientific Session 3: Molecular imaging

Wednesday, 13 October, 13:15 – 14:45 CEST

Speakers: Russell Ouellette, Benedetta Bodini, Paolo Preziosa, Bretta Russell-Schulz, Elena Herranz, Riccardo Galbusera

Chairs: Olga Ciccarelli, Bruno Stankoff

Conclusion: To benefit patients with MS, continuous validation of advanced quantitative neuroimaging techniques and promotion of their incorporation into the clinical setting are needed.

Novel and even more specific positron emission tomography (PET) tracers are currently being developed to determine the role and clinical relevance of components of the immune system.

Quantification of slowly expanding lesions (SEL) number and volume and microstructural damage, using T1-, T2-weighted and magnetisation transfer ratio (MTR) sequences, may identify relapsing and remitting MS patients at higher risk of long-term disability progression and secondary progressive MS conversion (SPMS).

What's New: Translocator protein 18-kDa (TSPO) PET allows specific and clinically relevant measurement of innate immune cell inflammation in MS. TSPOPET has demonstrated that chronic active lesions and diffuse innate immune cell activation is characteristic of patients who are entering a severe phase of their disease. Future targets for innate immune cell imaging include macrophage colony stimulating factor 1 receptor, P2Y12R and P2X7R.

In a 9-year longitudinal study, SEL burden and microstructural damage were associated with a high risk of 9-year Expanded Disability Status Scale (EDSS) worsening in MS. Lower baseline SEL MTR and T1-weighted intensity were significantly associated with higher risk of SPMS conversion.

Magnetic resonance spectroscopy (MRS) has revealed insights about the mechanisms of action of ocrelizumab in patients with relapsing MS and primary progressive MS over 1 year of follow-up in a clinical trial. Relapsing remitting MS trended toward increasing total N-acetyl-aspartate (axonal recovery) and primary progressive MS trended toward decreasing myo-inositol (declining inflammation).

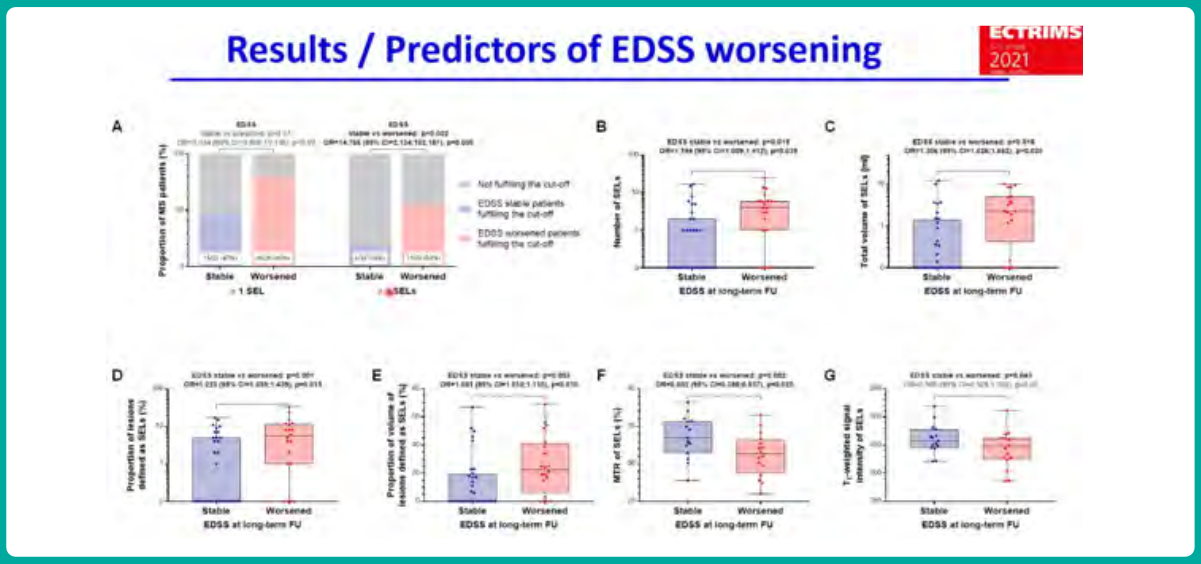
^{11}C-PBR28 magnetic resonance PET revealed *in vivo* inflammatory signal changes in meningeal brain tissue in patients with MS: diffuse and abnormally increased ^{11}C-PBR28 binding was observed in the cortex, juxtacortical and meningeal/parameningeal tissue. Increased TSPO levels in meningeal/parameningeal brain tissue were associated with worsening EDSS and symbol digital modalities test scores.

The quantitative magnetic resonance imaging (MRI) parameters myelin water fraction and radial diffusivity have been used for quantification of myelin integrity (white matter lesions and normal-appearing white matter) in patients with MS.

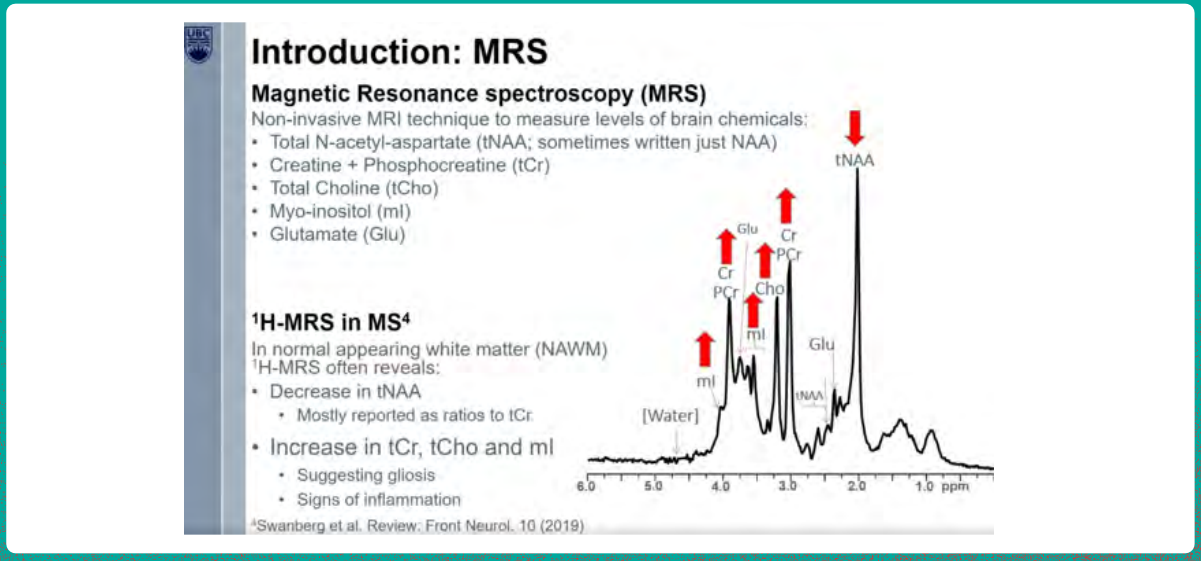
Background: MRI is a valuable clinical tool in MS and the only recommended imaging modality. Conventional MRI remains sensitive to MS pathology but unspecific to myelin. PET-based molecular imaging of myelin is a viable complementary approach. MRS, a non-invasive MRI technique, can be used to measure the levels of brain chemicals following treatment for MS.

Adaptive and innate immune systems are known to be central to the pathophysiological of MS, at both the acute and chronic stages of the disease. Advanced MRI techniques are being developed to measure chronic inflammation in lesions and leptomeningeal inflammation but need further validation in vivo.

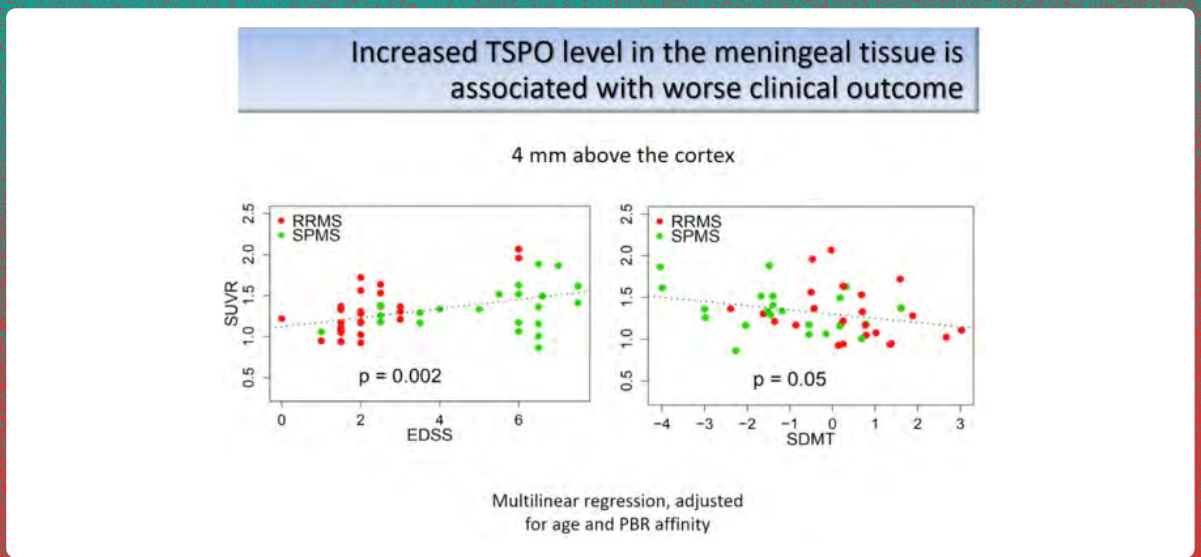
(Preziosa presentation)



(Russell-Schulz presentation)



(Herranz, presentation)



Imaging & Non-Imaging

Poster Tour 3 – Imaging and non-imaging biomarkers / Translational

Wednesday, 13 October, 16:45 – 17:30 CEST

Speakers: Patrick Vermersch, Marta Pengo, Christian Cordano, Floriana De Angelis, Laura Ferrè, Harald Hegen

Chair: Gabriel Bsteh

Conclusion: There is a need to develop better markers of disability progression in MS. Optical coherence tomography (OCT) measures, T-cell receptor repertoire, and the κ-free light chains (κ-FLC) index are promising candidates.

Age is a critical consideration in the design of clinical trials using atrophy in OCT as an outcome measure.

Further studies are needed to explore the correlation between T-cell receptor repertoire diversity and measures of disease activity and severity in patients with MS.

What's New: Results from the Exploring the Efficacy and Safety of Siponimod in Patients with Secondary Progressive MS (EXPAND OCT) substudy showed that siponimod preserved retinal thickness.

Microglia activation in the inner retina has been associated with and predictive of brain inflammatory disease activity in MS. Differences in the dynamics of retinal and cortical atrophy have been observed across the course of the disease in patients with MS from the EPIC (expression/genomics/proteomics, imaging, and clinical) study. OCT detected significant retinal thinning after 96 weeks in patients with secondary progressive MS from the MS Secondary Progressive Multi-Arm Randomization Trial (MS-SMART).

In other studies, a less diverse T-cell repertoire seems to be associated with a better outcome during follow-up in patients with relapsing remitting MS during first-line treatment (when using the no evidence of disease activity criterion). Also, in patients with early MS, a high κ-FLC index is an independent risk factor for an early second clinical attack.

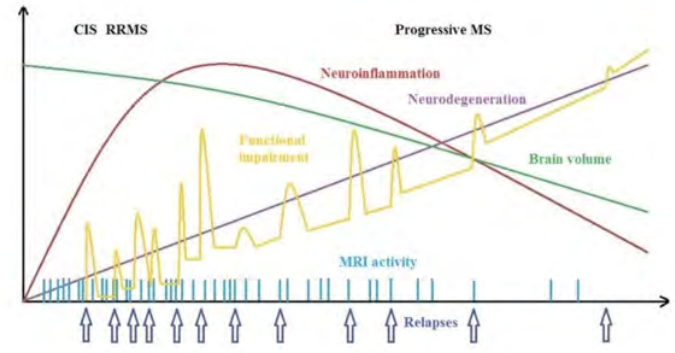
Background: Thinning of the retinal layers has been associated with MS-related disability and brain atrophy and is more pronounced in progressive MS than relapsing MS.

Microglia activation is widespread in both the white matter and grey matter of patients with MS. It has recently been hypothesised that silent damage of the retina is driven by activated microglia in MS and may be a potential inflammatory and prognostic biomarker.

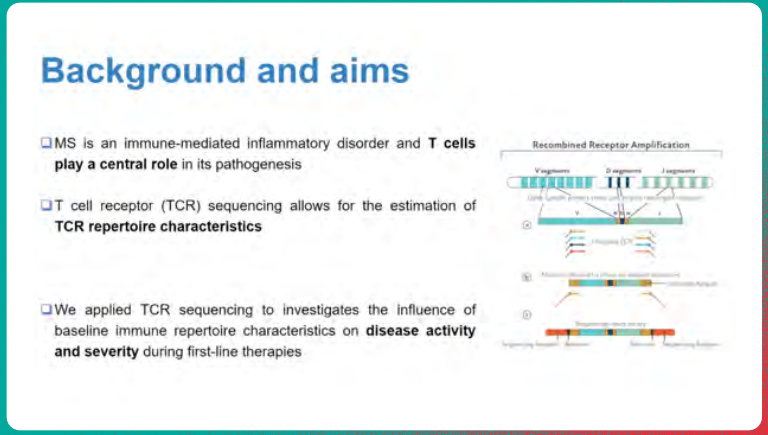
T cells play a central role in the pathogenesis of MS, and T-cell receptor sequencing has been used to investigate the influence of baseline immune repertoire characteristics on disease activity in MS patients during first-line therapies.

κ-FLC in the cerebrospinal fluid are also an emerging biomarker with high diagnostic accuracy in MS.

(Cordano presentation)



(Ferré presentation)



Biomarkers/Translational Therapy

Hot Topic 4: Clinical relevance versus statistical significance – critical appraisal of MS research

Wednesday, 13 October, 12:00 – 13:00 CEST

Speakers: Elena Hernandez Martinez, Florian Deisenhammer, Carmen Tur

Chairs: Anne Cross, Tobias Derfuss

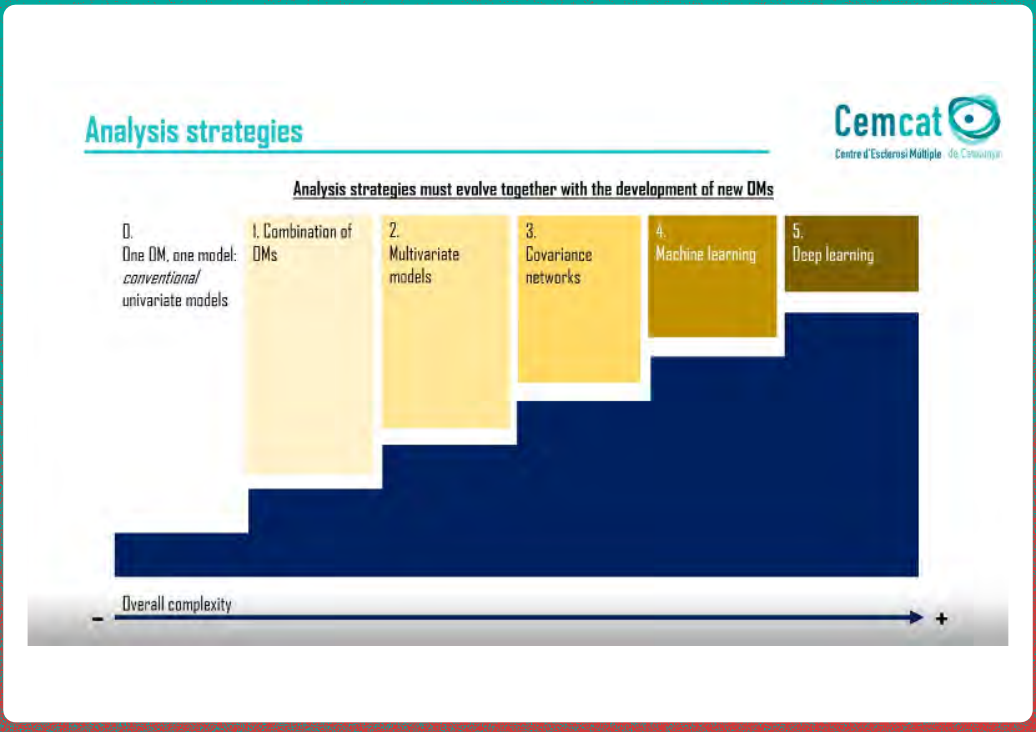
Conclusion: A 3-step process should be used to critically appraise clinical studies; internal validity, clinical relevance and generalisability. Regarding statistical analyses, confidence intervals (CIs) are much more informative than P-values and reaching statistical significance should not be the absolute goal of a clinical trial. Current clinical outcome measures are suboptimal and analysis strategies must be developed further as we enter the era of big data in MS.

What's New: When summarising a clinical study, the following should be assessed: estimate and 95% CI, methodology, consistency across endpoints and subgroups plus clinical relevance and generalisability. Clinical relevance should only be considered once internal validity of the study has been confirmed in terms of the experimental and analytical approaches used. Generalisability can be based on similarity of populations or the grounds for extrapolation. For marketing approval submissions, improvements in reported outcomes must be clinically relevant, not just statistically significant, and if novel measures are used then the threshold for clinical relevance must be clearly validated.

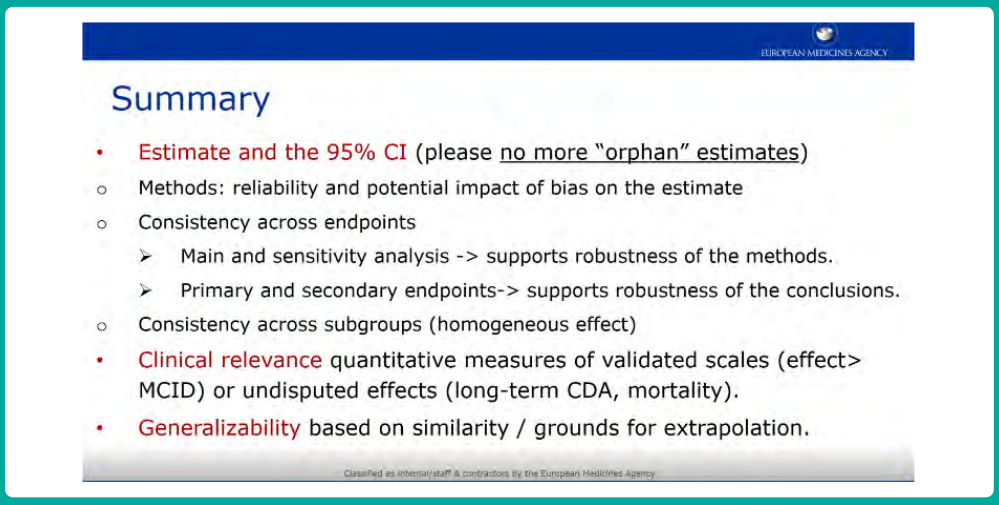
There are common misconceptions when interpreting P-values. A P-value in isolation is meaningless as it is highly dependent on the statistical and experimental approach taken. The entire process from experimental design to statistical analysis should be examined when assessing a study.

Background: Current clinical outcomes in MS research are not sensitive if analysed in isolation, and non-clinical outcomes are highly unspecific. The number of trial outcomes in MS has increased massively in recent years and now includes around a thousand variables. When assessing a clinical trial, the focus has often been on whether statistical significance is reached.

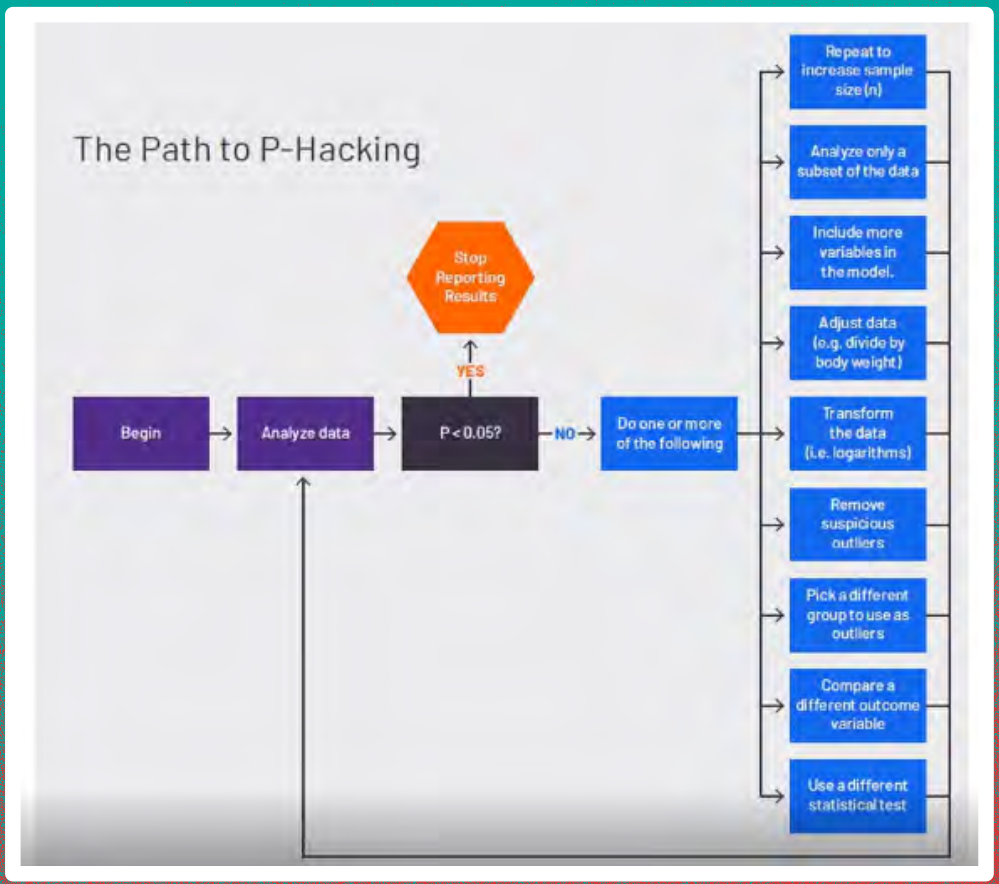
(Tur presentation)



(Hernandez Martinez presentation)



(Deisenhammer presentation)



Biomarkers/Translational Therapy

Scientific Session 4: Real world evidence data and MS registries

Wednesday, 13 October, 13:15- 14:45 CEST

Speakers: Jan Hillert, Helmut Butzkueven, Peter Alping, Camille Sabathé, Huah Shin Ng, Mattia Fonderico

Chairs: Dana Horakova, Maria Trojano

Conclusion: Analyses of MS patient registry data continue to provide and verify important real-world findings that are not possible with clinical trials. The potential reduction in precision of registry data versus clinical trial data is more than made up for in terms of patient numbers and range of patients. The addition of passive and active self-monitoring will increase the quantity and quality of patient registry data, and provide opportunities to identify elusive biomarkers.

What's New: The Big MS Data Network (BMSD) has been established to pool MS registry data from six countries and currently has data from almost 300,000 patients. Recent studies from the BMSD have shown increased discontinuations of disease-modifying therapies (DMTs) as new treatment options have entered the market, and better long-term disability outcomes when patients are treated earlier, in a much larger population than previous studies. Patient registries for MS are now looking to incorporate smartphone-based patient-reported quantitative measures with the aim of helping to identify a biomarker for progressive MS.

A study of the Swedish MS register found that in previously treatment-naïve patients, rituximab was associated with lower relapse risk and magnetic resonance imaging lesions than dimethyl fumarate, natalizumab and injectable therapies. However, EDSS at 3 years was similar to dimethyl fumarate and natalizumab, and only slightly higher for injectables.

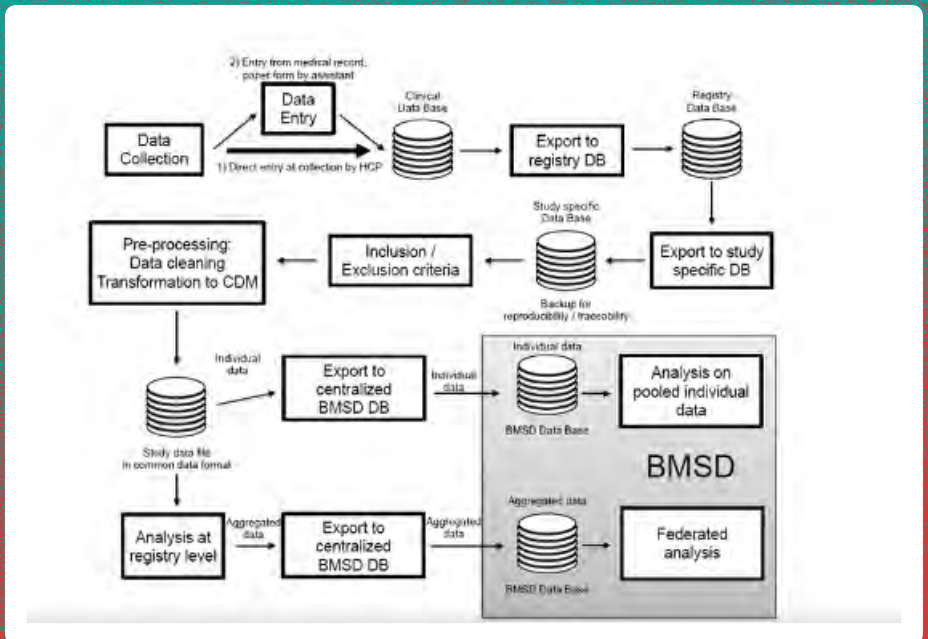
A dynamic scoring system has been developed and validated to help the decision to switch from first- to second-line treatment using data from the OFSEP cohort. The system calculates an individual hazard ratio and identified that patients who were younger at disease onset, had low EDSS at first-line treatment initiation, ≥1 relapse or ≥1 Gd-enhancing T1 lesion under first-line treatment will benefit most from switching treatment.

A study of health administrative data in Canada found that exposure to a DMT was generally associated with avoiding hospitalisation whereas DMT exposure was not associated with the number of physician visits.

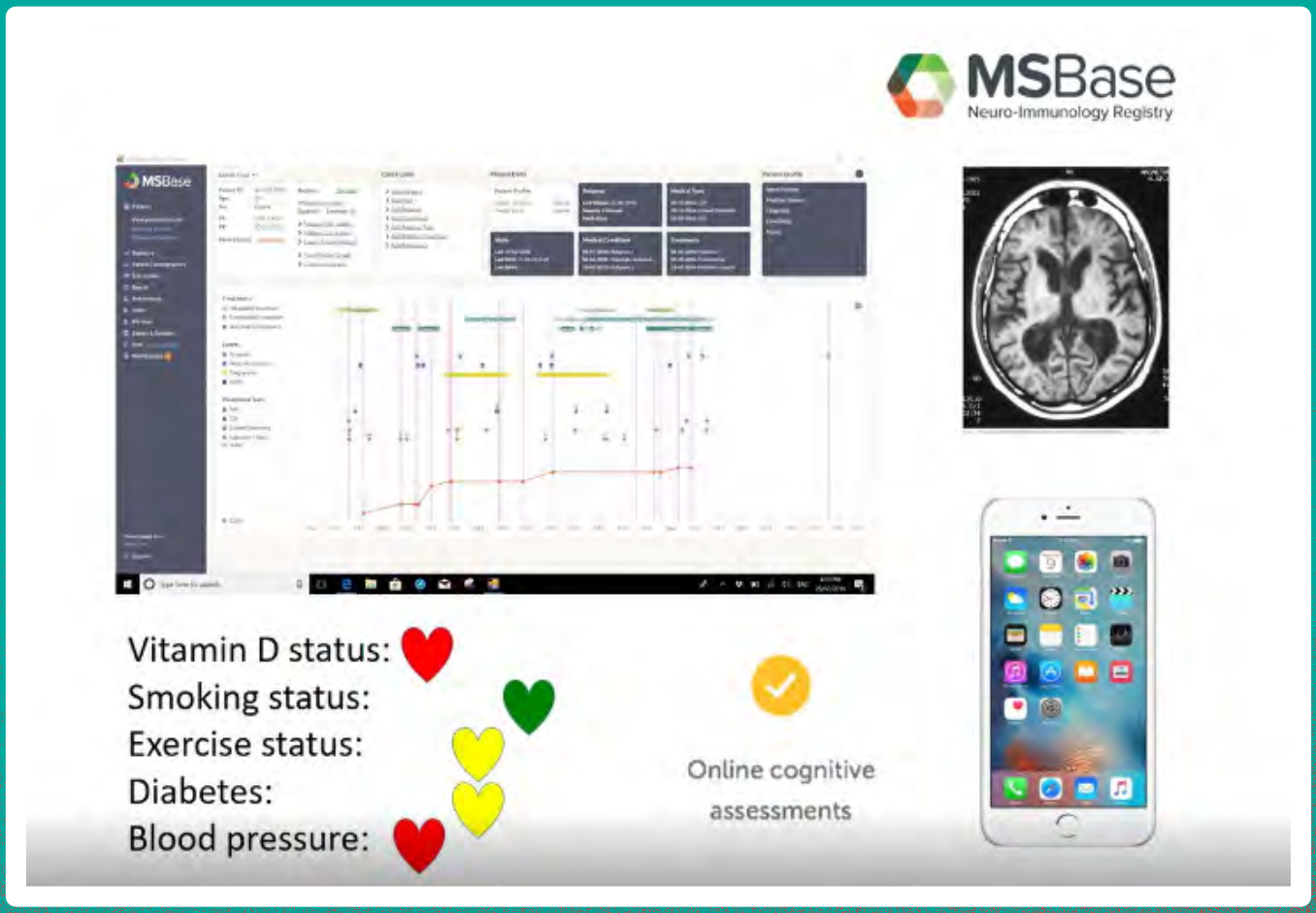
The Italian MS register provided data on disease progression independent of relapse activity, which was identified in approximately two thirds of patients with early relapsing MS.

Background: Current MS patient registries provide a source of real-world data at unprecedented scales. Real-world data offer direct comparisons across therapies and can capture treatment aspects that are missed in clinical trials.

Big MS Data Network (BMSD)
Pooling of MS registry data
(Hillert presentation)



The Dashboard of 21st century MS studies and care
(Butzkueven presentation)



Biomarkers/Translational Therapy

Poster Tour 4 - Therapy / Global views

Wednesday, 13 October, 16:45 – 17:30 CEST

Speakers: Mirko Capanna, Alexander Wuschek, Tim Spelman, Wan-Yu Hsu, Valentina Camera, Celia Oreja-Guevara

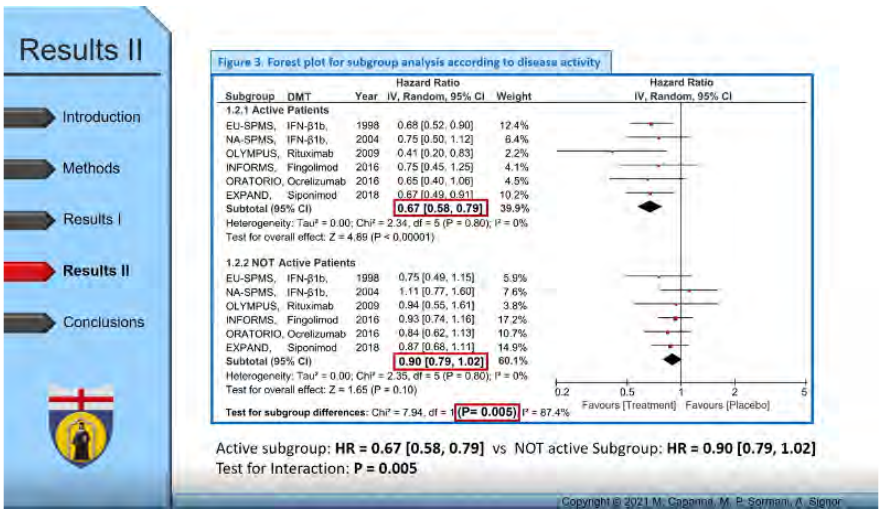
Chairs: Ellen Iacobaeus

Conclusion: Patients with primary MS and active disease may benefit more from disease modifying therapies (DMTs) in terms of disability progression than patients without active disease. Further research is needed to understand the reasons for incomplete B-cell depletion by ocrelizumab in some patients and the impact on patient outcomes. A strategy of treatment escalation in newly diagnosed patients should incorporate close monitoring to quickly identify patients with breakthrough disease. Melatonin supplements may offer a cheap and readily available way to alleviate sleep disturbances. COVID-19 vaccines are safe for patients with MS and effective in most patients.

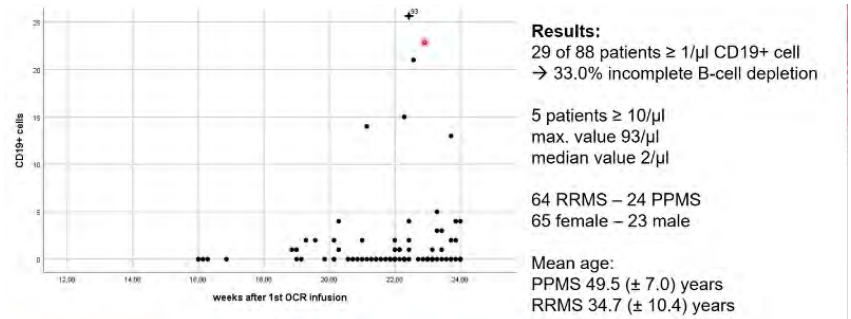
What's New: When stratifying patients with progressive MS by disease activity, effect of DMTs on time to confirmed disability progression was more favourable in patients with active disease than those with inactive disease. Incomplete depletion of B-cells 5 months after induction of ocrelizumab was observed in one-third of patients in a real-world study; higher body mass index was a significant predictor of incomplete B-cell depletion, but not body weight. Reduction in confirmed disability worsening was reported to be greater in a country that uses a strategy of immediate treatment with high efficacy DMTs versus a country that focuses on treatment escalation. Exogenous melatonin improved total sleep time in patients with sleep disturbance. Adverse events reported in patients with MS after receiving a COVID-19 vaccine are similar to those in healthy volunteers. Post-vaccination humoral responses varied and were lower in patients receiving B-cell-depleting DMTs than in patients receiving other DMTs. In patients with a longer duration since most recent dose of anti-CD20 therapy at time of vaccination, the impact on humeral response was lower due to B-cell repopulation.

Background: Only two treatments are currently approved for progressive MS, including ocrelizumab which depletes B-cells. Treatment strategies for newly diagnosed patients with MS can vary by country. People with MS often experience sleep disturbance. The recent widespread use of COVID-19 vaccines has raised questions over their safety and efficacy in patients with MS.

(Campanna presentation)



(Wuschek presentation)



Results:
29 of 88 patients ≥ 1/µl CD19+ cell
→ 33.0% incomplete B-cell depletion

5 patients ≥ 10/µl
max. value 93/µl
median value 2/µl

64 RRMS – 24 PPMS
65 female – 23 male

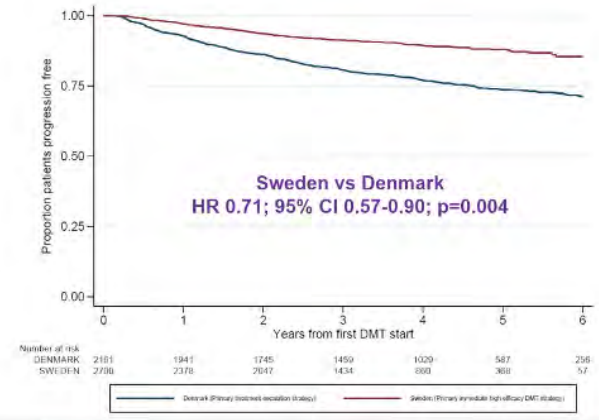
Mean age:
PPMS 49.5 (± 7.0) years
RRMS 34.7 (± 10.4) years

	complete B cell depletion	incomplete (≥ 1 CD19+ cell/µl)
patients [n]	59	29
RRMS [%]	74.6 %	69.0 %
female sex [%]	72.9 %	75.9 %
age [y]	38.5 ± 11.5	39.3 ± 12.1
pretreatment CD19+ cells/µl	308 ± 250	442 ± 356
BMI [kg/m²]	22.9 ± 4.0	27.3 ± 7.2

Statistically significant predictor:
BMI (R=.375; p=.002)

24-week confirmed disability worsening

(Spelman presentation)



Karolinska Institutet

Sweden = 29% reduction in rate of 24-week CDW

Humoral response to SARS-CoV-2 mRNA vaccines in patients treated with antiCD20 and fingolimod

(Oreja-Guevara presentation)

Ocrelizumab

Patient	Vaccine	First Shot	AB after 3 weeks	Second Shot	AB after 6 weeks	AB after 3 months	Comments
1	Pfizer	Jan 2021	-	Feb 2021	4783.7	1047.5	Washout 12 months
2	Moderna	Feb 2021	11	Mar 2021	11.6	6.8	
3	Pfizer	Feb 2021	1.2	Mar 2021	0	0	
4	Pfizer	Abril 2021	-	Mayo 2021	-	1.3	
5	Pfizer	Abril 2021	-	Mayo 2021		0.7	
6	Pfizer	Abril 2021	-	Mayo 2021	22203	4557	Washout 12 months
7	Pfizer	Abril 2021	0	Mayo 2021	0	0	
8	Pfizer	Abril 2021	0	Mayo 2021	0		
9	Pfizer	Abril 2021		Mayo 2021		8.6	
10	Pfizer	May 2021	3.4	Jun 2021	0	1	
11	Pfizer	May 2021	7140.3	Jun 2021	20441	14721	Covid hospitalized
12	Pfizer	May 2021	3.9	Jun 2021	13.9	-	
13	Pfizer	May 2021	0	Jun 2021	5.5	-	
14	Pfizer	Jun 2021	-	Jul 2021	2.1	0	
15	Pfizer	Jun 2021	17.2	Jul 2021	-	-	
16	Pfizer	Jun 2021	0	Jul 2021	16.5	48.9	
17	Pfizer	Jun 2021	2.2	Jul 2021	-	-	
18	Pfizer	Jul 2021	1.4	Ago 2021	1.4	-	
19	Pfizer	Jul 2021	-	Ago 2021	16.5	15	
20	Moderna	Ago 2021	-	Sept 2021	1.9	-	

Only 3 out of 20 patients treated with ocrelizumab developed antibodies:
Two had a washout period of 12 months between last dose of ocrelizumab and the first vaccine shot and one was hospitalized due to Covid19 infection.
6 vaccinated patients treated with rituximab had no antibody response.

4 of 5 patients treated with ofatumumab had antibody response

Fingolimod

Patient	Vaccine	First Shot	AB after 3 weeks	Second Shot	AB after 6 weeks	AB after 3 months
1	Pfizer	Jan 2021		Feb 2021	129.30	110.20
2	Pfizer	Jan 2021	0.4	Feb 2021	92.70	63.40
3	Pfizer	Apr 2021	9.6	May 2021	8.4	45.3
4	Pfizer	May 2021	1.6	Jun 2021	1.9	0.4
5 (covid)	Moderna	May 2021	4201.2	Jun 2021	6819.2	10512.40
6 (covid)	Pfizer	May 2021	28986	NO 2nd dose	21118	15931
7	Pfizer	May 2021	314.4	Jun 2021	236.7	141.4
8	Pfizer	May 2021	4.3	Jun 2021	138.7	80
9 (covid?)	Pfizer	May 2021	10042	Jun 2021	12907	6881.1
10	Pfizer	May 2021	-	Jun 2021	57.1	25.1
11 (covid)	Pfizer	Jun 2021	9795.5	Jul 2021	5957	3336
12 (covid?)	Pfizer	Jun 2021	931.5	Jul 2021	1869.9	912.3
13	Pfizer	Jun 2021	32.5	Jul 2021	38.6	33
14	Pfizer	Jun 2021	10.7	Jul 2021	402	1511.3
15	Pfizer	Jun 2021	-	Jul 2021	111.4	127.6
16	Pfizer	Jun 2021	0.3	Jul 2021	3.6	-

Four from 16 patients treated with fingolimod failed to develop a post-vaccination humoral response (< 50 AU/ml) , 7 had a low antibody response, 5 had a similar response to the healthy controls (3 of them with previous Covid-19 infection)

Ofatumumab

Patient	Vaccine	First Shot	AB after 3 weeks	Second Shot	AB after 6 weeks	AB after 3 months	comments
1 (covid)	Pfizer	may-21	3861.4	Jun 2021	4342.5	3987.3	
2 (covid)	Pfizer	Feb 2021		Mar 2021	2256.7	618.6	
3	Moderna	May 2021	5919.6	Jun 2021	4978.5		
4	PFIZER	Jul 2021	136.6	Aug 2021			Long treatment duration
5(covid)	Moderna	May 2021	4.8	Jun 2021	1.4		Long treatment duration