ECRIMS 2021 – Late Breaking News Oral Presentations

Free Communication 1: COVID-19

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Updated results of the COVID-19 in MS global data sharing initiative validate consistent associations of anti-CD20 and other reported risk factors with severe COVID-19 outcomes

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Background: As the COVID-19 pandemic continues, evidence-based clinical guidance for managing the care of people with multiple sclerosis (MS) is an ongoing concern. In recent months, data from cohorts of people with MS has indicated that certain demographic and clinical characteristics, including use of some disease-modifying therapies (DMTs), leads to worse outcomes from SARS-CoV-2 infection. The COVID-19 in MS global data sharing initiative, which now includes over 4,500 confirmed COVID-19 cases in people with MS, gives the opportunity to corroborate previous findings with greater certainty.

Methods: Clinician-reported data from 32 countries were aggregated into a dataset of 5,543 patients who had suspected or confirmed COVID-19. Demographic and clinical covariates were queried, alongside COVID-19 clinical severity outcomes. These outcomes (hospitalisation, admission to ICU, requiring artificial ventilation, and death) were assessed in patients with suspected/confirmed COVID-19 using multilevel mixed-effects logistic regression. All models were corrected for age, sex, EDSS, and MS type. DMTs were individually compared to glatiramer acetate (GA), as well as to pooled other DMTs and natalizumab.

Results: Of 5,543 patients in the clinician-reported dataset, 909 with suspected and 4,634 with confirmed COVID-19 were included in the analysis. Previous demographic findings were confirmed: male sex, older age, progressive MS, and higher disability were associated with worse outcomes from SARS-CoV-2 infection. Use of anti-CD20 DMTs (ocrelizumab and rituximab) was associated with worse COVID-19 outcomes. Compared to GA, ocrelizumab and rituximab were associated with increased risk of hospitalisation (aOR=1.61(95%CI=1.06-2.43); aOR=2.42(95%CI=1.54-3.81)) and ICU admission (aOR=3.13(95%CI=1.22-8.00); aOR=4.46(95%CI=1.64-12.09)). Rituximab was associated with increased risk of artificial ventilation (aOR=3.57(95%CI=1.38-9.20)); ocrelizumab showed a positive trend (aOR=1.86(95%CI=0.76-4.55). Rituximab showed a positive trend with increased risk of death (aOR=2.74(95%CI=0.68-11.09). Associations persisted on restriction to confirmed COVID-19 cases.

Conclusions: Analysing the largest international real world data set of people with MS who have suspected or confirmed COVID-19 confirms previous findings that male sex, older age, progressive
MS, higher disability, the use of anti-CD20 medication (ocrelizumab and rituximab) are associated with worse COVID-19 outcomes.

Disclosure
Steve Simpson-Yap: Nothing to disclose.
Ashkan Pirmani: Nothing to disclose.
Edward De Brouwer: Nothing to disclose.
Lotte Geys: Nothing to disclose.
Tina Parciani: Nothing to disclose.
Anne Helme: Anne Helme has no personal pecuniary interests to disclose, other than being an employee of MSIF, which receives income from a range of corporate sponsors, recently including: Biogen, Bristol-Myers Squibb (formerly Celgene), Genzyme, Med-Day, Merck, Mylan, Novartis, Roche
Nick Rijke: Nick Rijke has no personal pecuniary interests to disclose, other than being an employee of MSIF, which receives income from a range of corporate sponsors, recently including: Biogen, Bristol-Myers Squibb (formerly Celgene), Genzyme, Med-Day, Merck, Mylan, Novartis, Roche
Tomas Kalincik: Tomas Kalincik served on scientific advisory boards for Roche, Sanofi-Genzyme, Novartis, Merck and Biogen, steering committee for Brain Atrophy Initiative by Sanofi-Genzyme, received conference travel support and/or speaker honoraria from WebMD Global, Novartis, Biogen, Sanofi-Genzyme, Teva, BioCSL, and Merck and received research support from Biogen.
Jan Hillert: Jan Hillert has received honoraria for serving on advisory boards for Biogen, Celgene, Sanofi-Genzyme, Merck KGaA, Novartis and Sandoz and speaker’s fees from Biogen, Novartis, Merck KGaA, Teva and Sanofi-Genzyme. He has served as P.I. for projects, or received unrestricted research support from, Biogen, Celgene, Merck KGaA, Novartis, Roche and Sanofi-Genzyme. His MS research was funded by the Swedish Research Council and the Swedish Brain foundation.
Yves Moreau: Nothing to disclose.
Gilles Edan: Gilles Edan has received consulting/speaking fees/research support from Bayer, Novartis, Teva, Sanofi-Genzyme, Merck Serono, Biogen Idec, Roche
Tim Spelman: Tim Spelman served on scientific advisory boards for Biogen.
Robert McBurney: Accelerated Cure Project for MS (ACP) has received grants, collaboration funding, payments for use of assets, or in-kind contributions from the following companies: EMD Serono, Sanofi/Genzyme, Biogen, Genentech, AbbVie, Octave, GlycoMinds, Pfizer, MedDay, AstraZeneca, Teva, Mallinckrodt, MSDx, Regeneron Genetics Center, BC Platforms, and Genelge. ACP has also received funding from the Patient-Centered Outcomes Research Institute (PCORI) and the National MS Society (NMSS). Hollie Schmidt has received a consulting payment from Celgene, which has been donated to ACP.
Arnfin Bergmann: consulting fees from and advisory board/speaker/other activities for NeuroTransData; project management/clinical studies for and travel expenses from Novartis and Servier
Stefan Braune: fees for consulting, clinical studies and lectures from NeuroTransData, Novartis, Celgene, Biogen, CSL Behring, Alexander Stahmann: Alexander Stahmann has no personal pecuniary interests to disclose, other than being the lead of the German MS-Registry, which receives funding from a range of public and corporate sponsors, recently including: The German Innovation Fund (G-BA), The German MS Trust, The German Retirement Insurance, German MS Society, Biogen, Celgene (BMS), Merck, Novartis, Roche and Sanofi
Amber Salter: Statistical editor for Circulation: Cardiovascular Imaging
Bruce Bebo: Nothing to disclose.
Anneke van der Walt: Has received honoraria and unrestricted research funding from Novartis, Biogen, Roche, Merck and Sanofi.
Helmut Butzkueven: Institution (Monash University) received compensation for consulting, talks, and advisory/steering board activities from Alfred Health, Biogen, Genzyme, Merck, Novartis; research support from Biogen, Merck, MS Research Australia, National Health and Medical Research (Australia), Novartis, the Oxford Health Policy Forum, the Pennycook Foundation, Roche.
Juan I. Rojas: has received honoraria from Novartis as a scientific advisor. He has received travel grants and attended courses and conferences on behalf of Merck-Serono Argentina, Novartis Argentina
Ingrid van der Mei: Nothing to disclose.
Guilherme Sciaccia do Olival: Has received honoraria for lecturing and support for congress participation from Biogen, Merck, Novartis, Sanofi/Genzyme, EMS and Roche
Melinda Magyari: Melinda Magyari has served on scientific advisory board for Biogen, Sanofi, Roche, Novartis, Merck, Abbvie, has received honoraria for lecturing from Biogen, Merck, Novartis, Sanofi, Genzyme, has received research support and support for congress participation from Biogen, Genzyme, Roche, Merck, Novartis.
Ricardo Alonso: has received honoraria from Novartis as a scientific advisor. He has received travel grants and attended courses and conferences on behalf of Merck-Serono Argentina, Biogen Argentina, Genzyme Argentina, Roche Argentina and Novartis Argentina
Richard Nicholas: Has received honoraria from Novartis, Roche and Biogen for advisory boards
Anibal Chertoff: Nothing to disclose
Ana Zabalza: Travel expenses for scientific meetings from Biogen, Novartis, and Genzyme; speaking honoraria from Eisai; and a study grant from Novartis
Georgina Arrambide: Compensation for consulting services or participation in advisory boards from Sanofi, Merck and Roche; research support from Novartis; travel expenses for scientific meetings from Novartis, Roche, Stendhal, and ECTRIMS; speaking honoraria from Sanofi and Merck; and is a member of the
Effect of SARS-CoV-2 mRNA vaccination in multiple sclerosis patients treated with disease modifying therapies

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Introduction: In patients with Multiple Sclerosis (pwMS) disease-modifying therapies (DMTs) are known to affect immune response to antigens and possibly to SARS-CoV-2 vaccine. Therefore, post-vaccination serological assessments are needed to evaluate the effect of the vaccine on SARS-CoV-2 antibody response.

Objectives and aims: We designed a prospective multicenter cohort study enrolling pwMS who were scheduled for SARS-CoV-2 vaccination with mRNA vaccines (BNT162b2, Pfizer/BioNTech, Inc or mRNA-1273, Moderna Tx, Inc) to evaluate their effect on SARS-CoV-2 antibody response.

Methods: A blood collection for the measure of SARS-CoV-2 antibody before the first vaccine dose and 4 weeks after the second dose was planned, with a centralized and blinded serological assessment (electrochemiluminescence immunoassay, ECLIA, Roche Diagnostics).

Results: Preliminary data were collected on 780 pwMS (76% BNT162b2 and 24% mRNA-1273) who had pre- and 4-week post-vaccination blood assessments. 87 (11.2%) were untreated, 154 (19.7%) on ocrelizumab, 25 (3.2%) on rituximab, 85 (10.9%) on fingolimod and 404 (51.7%) on other DMTs. 677 patients (86.8%) had detectable post-vaccination antibodies. At multivariate analysis, the antibody response was systematically 3.5-fold higher antibody level than with the untreated patients. Vaccination with mRNA-1273 resulted in a 3.5-fold higher antibody level than with the untreated patients. Vaccination with mRNA-1273 resulted in a decrease, p < 0.001). These decreases were significantly reduced as compared to untreated patients. Vaccination with mRNA-1273 resulted in a significantly reduced antibody response to mRNA-1273 vaccine (p < 0.001).

Interpretation: In pwMS, anti-CD20 treatment and fingolimod led to a reduced humoral response to mRNA-based SARS-CoV-2 vaccination.
vaccines. As mRNA-1273 elicits 3.5-higher antibody levels than BNT162b2, this vaccine may be preferentially considered for patients under anti-CD20 treatment or fingolimod. Combining our data with those that will be produced by studying the cellular immune response to vaccines, and including clinical follow-up, will contribute to better define the most appropriate SARS-CoV-2 vaccine strategies in the context of DMTs and MS. At the time of the ECTRIMS presentation data on the full sample (about 2000 subjects) will be presented.

Disclosure
MPS reports grants from Roche, during the conduct of the study; personal fees from Biogen, Merck, Roche, Sanofi, personal fees from Novartis, Medday, Geneuro, Celgene, Mylan, outside the submitted work; MI reports consulting fees from Roche, Merck-Serono, Novartis, Sanofi-Genzyme, Biogen; AL has received personal compensation from Novartis, Sanofi Genzyme, Biogen, Merck, and Roche for public speaking and advisory boards. AL received funding for research by Fondazione Italiana Sclerosi Multipla, the Italian Ministry of Health, and the Italian Ministry of University; CC reports personal fees from Novartis, personal fees from Biogen Idec, personal fees from Almirall, personal fees from Merck Serono, outside the submitted work; DL reports consulting fees Roche, Biogen, Teva, Mylan, Sanofi-Genzyme, fees for advisory boards from Bristol-Celgene, Merck, Novartis, JR reports consulting fees from Sanofi, Biogen, Admirall; ADS reports personal consulting fees from Biogen, Novartis, Genzyme; MS reports research support and personal consulting fees from Merk, Sanofi, Novartis, Biogen, Roche; AU has received personal compensation from Novartis, Biogen, Merck, Roche and Sanofi Genzyme for public speaking and advisory boards. AU received funding for research by Fondazione Italiana Sclerosi Multipla, the Italian Ministry of Health and the European Community.

Background: With the new highly active drugs available for the treatment of Multiple Sclerosis (MS) patients, vaccination becomes an essential part of the risk management strategy. There is a need for a reference tool to aid professionals in deciding on the best vaccination strategy for their patients.

Objectives: To develop a European evidence-based consensus document for the vaccination strategy of people with MS.

Methods: A formal consensus methodology has been followed. A multidisciplinary working group composed of 14 MS experts, vaccine experts and patient representatives, and an external review group was established in September 2020. The working group agreed on the scope, questions, tasks and timeline. Clinical questions were formulated defining the population, interventions and outcomes. For each question, a systematic literature search was conducted considering published studies, guidelines and position statements. According to the Oxford Centre for Evidence-Based Medicine (OCEBM) Levels of Evidence, the quality of evidence was defined, and the recommendations were formulated based on the quality of evidence and the risk-benefit balance.

Results: A literature search and a narrative description of the evidence has been conducted for seven questions, encompassing vaccine safety, vaccine effectiveness, global vaccination strategy and vaccination in subpopulations (pediatric, pregnant women, elderly and international travelers). A total of 60 recommendations were
proposed to the working group for the first round of consensus, of which 47 were validated without further modification and 6 with minor rewording. A total of 7 statements without agreement or with major rewording were voted in a second round, reaching consensus in 6 of them. **Conclusions:** A total of 59 recommendations on the best vaccination strategy for patients with MS according to current evidence and expert knowledge have been issued. This is the first European consensus on vaccination in patients with MS and will contribute to the homogeneity of the immunization of MS patients.

**Disclosure**

SOR has received speaking and consulting honoraria from Genzyme, Biogen-Idec, Novartis, Roche, Excemed and MSD; as well as research support from Novartis. SR has received speaking honoraria or scientific advisory fees from Merck, Novartis and Biogen. MPA has served on Scientific Advisory Boards for Biogen, Novartis, Roche, Merck, Sanofi Genzyme and Tева; has received speaker honoraria from Biogen, Merck, Sanofi Genzyme, Roche, Novartis and Tева; has received research grants for her Institution from Biogen, Merck, Sanofi Genzyme, Novartis and Roche. She is co-editor of the Multiple Sclerosis Journal and Associate Editor of Frontiers in Neurology. MC has received compensation for consulting services and speaking honoraria from GSK, Novartis, Sanofi Pasteur, MSD, Pfizer and Seqirus. MF is Editor-in-Chief of the Journal of Neurology, Associate Editor of Human Brain Mapping, Associate Editor of Radiology, and Associate Editor of Neurological Sciences; received compensation for consulting services and/or speaking activities from Alexion, Almirall, Bayer, Biogen, Celgene, Eli Lilly, Genzyme, Merck-Serono, Novartis, Roche, Sanofi, Takeda, and Tева Pharmaceutical Industries; and receives research support from Biogen Idec, Merck-Serono, Novartis, Roche, Tева Pharmaceutical Industries, Italian Ministry of Health, Fondazione Italiana Sclerosi Multipla, and ARISLA (Fondazione Italiana di Ricerca per la SLA). BH has served on scientific advisory boards for Novartis; he has served as DMSC member for AllergyCare, Polipharma and TG therapy; he or his institution have received speaker honoraria from Desitin, His institution received research grants from Regeneron for multiple sclerosis research. He holds part of two patents; one for the detection of antibodies against KIR4.1 in a subpopulation of patients with multiple sclerosis and one for genetic determinants of neutralizing antibodies to interferon. All conflicts are not relevant to the topic of the study. RJ has received advisory board honoraria received from Bristol-Myers Squibb. MM has served on scientific advisory board, as consultant for , received support for congress participation or speaker honoraria from Biogen, Sanofi, Roche, Novartis, Merck, Abbvie, Alexion, BMS .The Danish MS Registry received research support from Biogen, Genzyme, Roche, Merck, Novartis. COG has received speaking and consulting honoraria from Biogen-Idec, Sanofi-Genzyme, Novartis, Merck, Tева, Roche, Taksela and BMS. AS has received honoraria or consultancy fees for participating to advisory boards, giving educational lectures and/or travel and registration coverage for attending scientific congresses or symposia from F. Hoffmann-La Roche Ltd, Sanofi-Genzyme, Merck-Serono, Novartis, Teva, Biogen Idec/Gen Pharma of Turkey and Abdi Ibrahim İlaç. SV received grants, personal fees and non-financial support from Biogen, grants, personal fees and non-financial support from Sanofi-Genzyme, grants, personal fees and non-financial support from Merck, grants, personal fees and non-financial support from Novartis, grants, personal fees and non-financial support from Roche. MT has received compensation for consulting services and speaking honoraria from Almirall, Bayer Schering Pharma, Biogen-Idec, Genzyme, Merck-Serono, Novartis, Roche, Sanofi-Aventis Viela-Bio and Tева Pharmaceuticals. CL, MFF and YH report no disclosures.

**Scientific Session 18: Late Breaking News**

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**Comparing humoral immune response to SARS-CoV2 vaccines in multiple sclerosis and healthy controls: an Austrian multi-center study**

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**Background:** Vaccination against SARS-CoV2 is unanimously recommended for patients with multiple sclerosis (MS), although some disease-modifying treatments (DMT) might limit immune response. However, data informing on differences in efficacy and safety of available vaccines in MS patients are scarce.

**Objective:** To compare magnitude and success rate of humoral immune response to SARS-CoV2 vaccines in patients with MS and healthy individuals.

**Methods:** In this multicenter prospective observational study on 467 MS patients and 124 healthy controls, SARS-CoV-2 IgG response was measured using anti-spike protein-based serology 3 months after the first dose. The primary endpoint was defined as the proportion of patients developing protective antibodies, secondary endpoints included antibody titer, efficacy and safety parameters.

**Results:** Preliminary analyses show that 89.9% of MS patients developed protective levels of anti-SARS-CoV-2 IgG antibodies compared to 97.6% in healthy controls. Positivity rate in patients on immunosuppressive DMT (methotrexate or mycophenolate mofetil) was significantly lower (63.8%, p < 0.001) than in patients without DMT (91.7%) or on immunomodulatory DMT (92.9%; interferon beta, glatiramer acetate, dimethyl fumarate, teriflunomide). Specifically, seroconversion was lowest under CD20mAb (55.2%) followed by cladribine (56.1%), siltuximab (73.9%) and azathioprine (96.3%). Detailed analyses reporting antibody titer levels and seroconversion rates will be reported at ECTRIMS 2021.

**Conclusions:** Humoral response to SARS-CoV2 vaccines in MS patients is generally excellent. While reduced by immunosuppressive DMT, most importantly by B-cell depleting CD20mAb, protective humoral response is still expected in the majority of patients.
Early predictors of disability in paediatric multiple sclerosis: evidence from a multi-national cohort

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Introduction: Early recognition of markers of faster disability progression in paediatric-onset multiple sclerosis (POMS) is important for treatment decisions at the earliest possible time after symptoms onset.

Objectives: We sought to identify the early predictors of disability progression in a multi-national cohort of patients with POMS, considering the potential for commencing high-efficacy disease-modifying therapies (DMTs).

Methods: We identified patients who were <18 years at the onset of MS symptoms from the global MSBase registry. Patients with first neurological assessment within 12 months from symptoms onset were included. The variables examined as predictors of future MS Severity Score (MSSS; disability ranked by disease severity) were: age at symptoms onset, EDSS score, relapse phenotypes and frequency during the first 12 months. The analyses were adjusted for cumulative proportion of time on high-efficacy DMTs. A Bayesian log-normal generalized linear mixed model was used to analyse the longitudinal data.

Results: 672 patients (70% female) contributing 9357 visits were included. The median (quartiles) age at symptoms onset was 16 (15-17) years. Older age at symptoms onset (exp(β)=1.09, 95% CI [1.03,1.16]), higher EDSS score (1.32 [1.21,1.45]), and frequent relapses (1.09 [1.00,1.19]) during the first 12 months were associated with higher MSSS. Complete recovery from first relapse (0.78 [0.63,0.96]) and having a brainstem relapse (0.79 [0.67,0.92]) were associated with lower MSSS. Interestingly, MSSS was reduced by 4% for each unit increase in the proportion of time on high-efficacy DMTs (0.96 [0.93,0.99]).

Conclusions: MS symptoms presented later in the childhood, frequent relapses, and higher disability during the first year predicted significant worsening in disability in patients with POMS. Persistent treatment with high-efficacy DMTs was associated with reduced rate of disability progression.

Keywords: paediatric multiple sclerosis, disease-modifying therapies, Bayesian
Disclosure
Sifat Sharmin has nothing to disclose.
Charles Malpas has nothing to disclose.
Izanne Roos served on scientific advisory boards, received conference travel support and/or speaker honoraria from Roche, Novartis, Merck and Biogen.
Ibrahim Diafli has nothing to disclose.
Raed Alroughani received honoraria as a speaker and for serving on scientific advisory boards from Bayer, Biogen, GSK, Merck, Novartis, Roche and Sanofi-Genzyme.
Serkan Ozakbas has nothing to disclose.
Guillermo Izquierdo received speaking honoraria from Biogen, Novartis, Sanofi, Merck, Roche, Almirall and Teva.
Sara Eichau received speaker honoraria and consulting fees from Biogen Idec, Novartis, Merck, Bayer, Sanofi Genzyme, Roche and Teva.
Dana Horakova received speaker honoraria and consulting fees from Biogen, Merck, Roche, Roche, Sanofi Genzyme, and Novartis, as well as support for research activities from Biogen and Czech Ministry of Education [project Progres Q27/LF1].
Eva Kubala Havrdova received honoraria/research support from Biogen, Merck Serono, Novartis, Roche, and Teva; has been a member of advisory boards for Actelion, Biogen, Celgene, Merck Serono, Novartis, and Sanofi Genzyme; and has been supported by the Czech Ministry of Education research project PROGRES Q27/LF1.
Francesco Patti received speaker honoraria and advisory board fees from Almirall, Bayer, Biogen, Celgene, Merck, Novartis, Roche, Sanofi-Genzyme and TEVA. He received research funding from Biogen, Merck, FISM (Fondazione Italiana Sclerosi Multipla), Reload Onlus Association and University of Catania.
Murat Terzi received travel grants from Novartis, Bayer-Schering, Merck and Teva; has participated in clinical trials by Sanofi Aventis, Roche and Novartis.
Cavit Boz received conference travel support from Biogen, Novartis, Bayer-Schering, Merck and Teva; has participated in clinical trials by Sanofi Aventis, Roche and Novartis.
Bassam Yamout has nothing to disclose.
Samia J. Khoury has nothing to disclose.
Marco Onofrj has nothing to disclose.
Aysun Soysal has nothing to disclose.
Riadh Gouider has nothing to disclose.
Ibrahima Diouf has nothing to disclose.
Maria Jose Sa has nothing to disclose.
Guillermo Izquierdo received speaking honoraria from Biogen, Novartis, Sanofi, Merck, Roche, Almirall and Teva.
Maria Pia Amato received honoraria as a consultant on scientific advisory boards by Biogen, Bayer-Schering, Merck, Teva and Sanofi-Aventis; has received research grants by Biogen, Bayer-Schering, Merck, Teva and Novartis.
Yara Fragosso has nothing to disclose.
Tomas Kalincik served on scientific advisory boards for BMS, Roche, Sanofi Genzyme, Novartis, Merck and Biogen, steering committee for Brain Atrophy Initiative by Sanofi Genzyme, received conference travel support and/or speaker honoraria from WebMD Global, Novartis, Biogen, Sanofi-Genzyme, Teva, BioCSL and Merck and received research or educational event support from Biogen, Novartis, Genzyme, Roche, Celgene and Merck.
Funding
This study was funded by the NHMRC [grant 1129189 and fellowship 1140766]. The MSBase Foundation is a not-for-profit organization that receives support from Merck, Biogen, Novartis, Roche, Bayer Schering, Sanofi Genzyme, and Teva Pharmaceutical Industries. The study was conducted separately and apart from the guidance of the sponsors.

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[11C]fluromazenil positron emission tomography in multiple sclerosis: model validation and clinical applicability in cognitive impairment
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Background: Cognitive impairment affects up to 65% of MS patients and is hypothesized to relate to changes in the GABAergic system. Here we studied changes on [11C]fluromazenil Positron Emission Tomography ([11C]FMZ PET), a measure of the GABAergic system, in relation to cognitive status in MS.

Aims: To determine the optimal metabolite corrected plasma input model for analysis of [11C]FMZ PET data in MS. Second, to compare the pharmacokinetic outcomes between healthy controls (HCs), cognitively preserved (CP) and impaired (CI) MS patients.

Methods: Fifteen MS patients (mean age 42.5 ± 10.2 years, 11 females, 14 RRMS, 1 SPMs) and 8 HCs (mean age 39.6 ± 12.0 years, 6 females) underwent 60 minutes of dynamic scanning on a Philips Ingenuity TOF 128 PET/CT scanner. 370 MBq of [11C]...
FMZ was administered to generate input-functions. Dynamic PET images were segmented and projected onto lesion-corrected, 3D-T1 weighted MRI scans to generate time-activity curves (TACs). One-tissue, two-compartment (1T2K_VB) and two-tissue, four-compartment models (2T4K_VB) were compared with Akaike information criterion (AIC). For the best model, influx rate (Kᵢ) and volume of distribution (Vᵢ) were determined for 7 brain areas relevant for cognition: superior frontal, fusiform and parahippocampal gyrus, hippocampus, thalamus and anterior and posterior cingulate cortex. Finally, neuropsychological testing (adjusted BRB-N) was used to classify patients as CI (when scoring \( z \leq -1.5 \) on \( \geq 2/9 \) tests) or as CP when not fulfilling CI criteria. ANOVA’s and independent t-tests were used to compare groups.

**Results:** The 1T2K_VB model had slightly favorable AIC values (50.3%) and \( Vᵢ \) was highly correlated among both models (Pearson’s \( r = .98 \)), making the simpler 1T2K_VB the optimal model. In MS, \( Kᵢ \) was lower than in HCs (P=.02), while \( Vᵢ \) was higher (P=.002). When comparing CI (N=10) and CP (N=5) patients to HCs, CI patients had lower \( Kᵢ \) values than HCs (P=.001) and CP patients (P=.006). \( Vᵢ \) values were higher in both patient groups compared to controls (P=.007).

**Conclusion:** The 1T2K_VB was the preferred model for analysis of \([11C]FMZ\) data in MS. \( Kᵢ \) and \( Vᵢ \) values were altered in MS, which may be related to neurodegeneration or –inflammation. A next step is to investigate whether these changes are a reflection of specific GABA-binding alterations to further unravel disease mechanisms underlying cognitive impairment in MS.

**Disclosure**

M. Huiskamp is supported by the Dutch MS Research Foundation, grant nr. 16-954b.

B.N.M. van Berckel: nothing to disclose

R. Boellaard: nothing to disclose

L.R.J. de Ruiter: nothing to disclose

J.J.G. Geurts is an editor of Multiple Sclerosis Journal. He serves on the editorial boards of Neurology and Frontiers of Neurology and innovation. He has served as a consultant for Merck-Serono, Biogen, Novartis, Genzyme and Teva Pharmaceuticals.

M.M. Yaqub: nothing to disclose

H.E. Hulst receives research support from the Dutch MS Research Foundation and serves as a consultant for Sanofi Genzyme, Merck BV, Biogen Idec and Novartis.

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**Introduction:** While the humanized anti-CD20 (aCD20) monoclonal antibody ocrelizumab is highly efficacious in limiting new MS disease activity, a small proportion of patients develop new disease activity early (typically 3–6 months) after treatment and then remain in remission with ongoing treatment. Assessing early cellular immune profiles and their association with such transient disease activity may provide a window into MS relapse biology.

**Methods:** Phenotypic and functional immune profiles were comprehensively assessed by multi-parametric flow cytometry in high-quality cryopreserved PBMC obtained from two independent, well-characterized (Discovery and Validation) MS cohorts, prior to and following ocrelizumab initiation and analyzed in relation to disease activity.

**Results:** The single-center Discovery cohort recruited patients with RRMS and PPMS, never previously exposed to disease-modifying
therapy (n=23), while the multi-center Validation cohort focused on 35 patients with RRMS. Anti-CD20 initiation decreased both CD4+ and CD8+ effector memory, pro-inflammatory cytokine-producing and central nervous system (CNS)-trafficking T cells, and mediated the predicted depletion of T cells expressing CD20 (all confirmed in the validation cohort). Treatment-associated changes in pro-inflammatory CD8+ T cells could be fully explained by removal of pre-treatment CD20-expressing CD8+ T cells, while treatment-associated changes in pro-inflammatory CD4+ T cells could only partially be attributed to direct removal of pre-treatment CD20-expressing CD4+ T cells. Remarkably, lower treatment proportions of circulating CD20-expressing CD8+ T cells were strongly correlated with the numbers of pre-treatment Gadolinium-enhancing lesions, and also associated with early disease activity observed after aCD20 initiation.

Conclusion: Our study provides novel insights into both the mode of action of aCD20 and mechanisms underlying MS relapse biology. We distinguish the impact of aCD20 on CD4+ and CD8+ T cells (largely direct removal of CD20-expressing cells), versus the impact of aCD20 on CD4+ T cells (a combination of direct removal, and indirect effects, presumably through depletion of B cells resulting in their diminished in vivo interactions with the CD4+ T cells). The strong inverse correlation with disease activity suggests that CD20-expressing CD8+ T cells leaving the circulation (possibly to the CNS) participate in early encephalitogenic events involved in MS relapse development.

Disclosure

K. Shinoda, R. Li, A. Rezk, I. M. et al. have nothing to declare. J. L. Bennett has received personal fees and non-financial support from Chugai Pharmaceutical, Viela Bio/Horizon Therapeutics, Equilium, Frequency Therapeutics, Mitsubishi-Tanabe, Reistone Bio, Abbvie, Clene Neuroscience, Alexion, Genentech, and Roche; and grants from Mallinckrodt and Novartis. H.-C. von Büdingen is an employee of F. Hoffmann-La Roche Ltd. R. L. Carruthers is Site Investigator for studies funded by Roche, Novartis, MedImmune, EMD Serono and receives research support from Teva Innovation Canada, Roche Canada and Vancouver Coastal Health Research Institute. R.C. has received honoraria from Roche, EMD Serono, Sanofi, Biogen, Novartis, and Teva. K. Edwards has received research/grant support from Biogen, Sanofi Genzyme, F. Hoffmann-La Roche Ltd and Genentech, Inc. and Novartis. R. Fallis has nothing to declare. P. S. Giacomini has received research support from EMD Serono and Hoffmann-La Roche Ltd. He has received honoraria for speaking and advisory board participation from Actelion, Allergan, Biogen Idec, EMD Serono, Sanofi Genzyme, Merz, Novartis, Pendopharm, F. Hoffmann-La Roche Ltd and Teva Neuroscience and has acted as a site investigator for clinical trials for Actelion, Alexion, Biogen Idec, EMD Serono, Sanofi Genzyme, GSK, Novartis, Ono, F. Hoffmann-La Roche Ltd and Teva Neuroscience. He also serves as a scientific advisor for Innomed Neuroscience. B. M. Greenberg has received consulting fees from Alexion, Novartis, EMD Serono, Viela Bio, Genentech/Roche, Greenwhich Biosciences, Axon Advisors, Rubin Anders, ABCAM, Signant, IQVIA, Sandoz, Druggability/Technologies, Genzyme, Immunovant, and PRIME Education. He has received grant funding from PCORI, NIH, NMSS, The Siegel Rare Neuroimmune Association, Clene Nanomedicine and the Guthy Jackson Charitable Foundation for NMO. He serves as an unpaid member of the board of the Siegel Rare Neuroimmune Association. He receives royalties from UpToDate. D. A. Hafler has in the past 10 years consulted for the following companies: Bayer, Biohaven Pharmaceuticals, Bristol-Myers Squibb, Compass Therapeutics, Eisai, EMD Serono, Genentech, Inc., Juno Therapeutics, McKinsey & Co., MedImmune/AstraZeneca, Mylan Pharmaceuticals, Neurophage Pharmaceuticals, NKTC Therapeutics, Novartis, Proclara Biosciences, Questcor Pharmaceuticals, F. Hoffmann-La Roche Ltd, Sage Therapeutics, Sanofi Genzyme, Toray Industries and Versant Venture; has received generous support by grants from the National Institutes of Health (U10 AI089992, R2S NS079193, P01 AI073748, U24 AI11867, R01 AI22220, UM 1HG009390, P01 AI039671, P50 CA121974, R01 CA227473) and the National Multiple Sclerosis Society (CA 1061-A-18, RG-1802-30153); is also supported by grants from the National Institute of Neurological Disorders and Stroke and the Nancy Taylor Foundation for Chronic Diseases and has received funding for his laboratory from Bristol-Myers Squibb, Genentech, Inc., Novartis Questcor, Sanofi Genzyme and Race to Erase MS. C. Ionete has received consulting fees from EMD Serono and Sanofi Genzyme and has received search support from F. Hoffmann-La Roche Ltd and Genentech, Inc., Biogen and Sanofi Genzyme. U. Kaunzner has nothing to declare. C. Lock has served on scientific advisory boards or as a speaker for Biogen, Sanofi, EMD Serono, Alexion, and Bristol-Myers Squibb, and has done consulting for InterX Inc and Diagnose Early. E. Longbrake has received honoraria for consulting from Genentech, Inc., Genzyme, Alexion, and Biogen, and research funding from the National Institutes of Health (23107624), Genentech, Inc. and Race to Erase MS. G. Pardo has served on advisory boards and/or speaker bureaus for Biogen, Celgene/Bristol Myers Squibb, EMD Serono, Genentech, Inc., F. Hoffmann-La Roche Ltd, Novartis, Sanofi Genzyme, Greenwich Biosciences, Teva, and VielaBio/Horizon. F. Piehl has received research grants from Biogen, Genzyme, Merck KGaA and Novartis, and fees for serving as chair of DMC in clinical trials for Parexel. M. S. Weber receives research support from the Deutsche Forschungsgemeinschaft (WE 3547/5-1), Novartis, Teva, Biogen Idec, F. Hoffmann-La Roche Ltd, Merck and the ProFutura Programm of the Universitätsmedizin Göttingen; is serving as an editor for PLoS One and has received travel funding and/or speaker honoraria from Biogen Idec, Merck Serono, Novartis, F. Hoffmann-La Roche Ltd, Teva, Bayer and Genzyme. T. Ziemssen received personal compensation from Almirall, Biogen, Bayer, Celgene, Novartis, Roche, Sanofi, Teva for the consulting services and additional financial support for the research activities from Biogen, Novartis, Teva, and Sanofi. J. M. Gelfand has received research support from UCSF from Genentech, Inc., and service contract support from UCSF from MedDay; has received consulting fees from Biogen and Alexion and has also received personal compensation for medical legal consulting. A. H. Cross has received fees or honoraria for consulting for Biogen, Celgene/Bristol Myers Squibb, EMD Serono, F. Hoffmann-La Roche Ltd, Genentech, Inc., Novartis TG Therapeutics, and received fees for serving on scientific advisory boards and reviewing grants for the Conrad N. Hilton Foundation and Race to Erase MS. B. Cameron, B. Musch, X. Jia, C. T. Harp, and A. Herman are employees of Genentech, Inc and shareholders of F. Hoffmann-La Roche Ltd. R. Winger is an
Neuregulin-1 facilitates remyelination by promoting the reparative properties of macrophages and microglia in animal models of multiple sclerosis

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Introduction: Failure of remyelination underlies the progressive nature of demyelinating diseases such as multiple sclerosis (MS). Macrophages and microglia are crucially involved in the formation and repair of demyelinated lesions. The repair of MS lesions requires the clearance of cholesterol-rich myelin debris by microglia and macrophages and the switch from a pro-inflammatory to an anti-inflammatory lesion environment. Therefore, targeting a disease-resolving phenotype in microglia and macrophages in demyelinating lesions could support remyelination in chronic lesions.

Objectives: Neuregulin-1 (Nrg-1), an important trophic factor involved in development of neural cells and myelin formation, is significantly declined in MS lesions. We hypothesized that bioavailability of Nrg-1 will foster oligodendrocyte replacement and remyelination by enhancing the microenvironment of demyelinating lesions.

Aims: To investigate the role and efficacy of Nrg-1 in promoting remyelination through modulation of microglia and macrophages in MS lesions.

Methods: We used preclinical experimental autoimmune encephalomyelitis (EAE) and cuprizone (CPZ) mouse model of MS. Primary mouse microglia, oligodendrocyte precursor cells (OPCs), bone marrow derived macrophages (BMDMs) have been used for in vitro studies.

Results: We show that restoring Nrg-1 levels in demyelinating lesions of the spinal cord promotes pro-regenerative phenotype of microglia and macrophages that is correlated with a significant increase of myelin index (g-ratio) in Nrg-1 treated EAE animals accompanied by axonal preservation. Mechanistically, Nrg-1 exerts its effect via modulation of phagocytic activity of microglia and macrophage in vitro. Moreover, conditioned media from activated microglia and macrophages treated with Nrg-1, promoted maturation of OPCs. This was due to enhanced lipid metabolism in microglia and macrophages under Nrg-1 treatment leading to efflux of myelin promoting fatty acids. These in vitro observations were further corroborated by our findings in CPZ model of progressive demyelination, in which Nrg-1 therapy created a more permissive environment for oligodendrocyte differentiation, maturation and remyelination.

Conclusions: These findings identify a novel mechanism of Nrg-1 in promoting remyelination in progressive demyelinating conditions, and introduces the promise of Nrg-1 treatment as a potential therapeutic strategy for myelin repair and axon preservation in progressive MS.

Decline of neural stem cell resilience in multiple sclerosis

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Introduction: Multiple sclerosis (PMS) is a chronic demyelinating disease of the central nervous system, which currently lacks effective therapies that provide regeneration and stop disease progression. A suggested link is anticipated between the development of progressive MS (PMS) and ageing, as suggested by recent work identifying hallmarks of cellular senescence in numerous cell types both ex vivo, in vitro with patient cell lines, and in vivo in the post mortem MS brain.

Objectives: Using a new inducible system, that directly reprograms human fibroblasts into induced NSCs (iNSCs), we aim to thoroughly characterise control and PMS patient iNSCs and progenies towards the development of a 2D and 3D in vitro model system that can be genetically manipulated using CRISPR technology. Using this model system, we aim to identify the key mechanisms driving disease progression and accumulation of irreversible damage in PMS.

Methods: We have generated stably expandable iNSC lines from patients with PMS and age-matched controls, and characterised these cells for senescence markers, phenotyped for NSC behaviour, performed bulk RNA sequencing and metabolomics, and single cell RNA and ATAC sequencing in vitro.

Results: Preliminary analysis of iNSCs and astroglial progenies have revealed a disease-associated (DA) senescent phenotype, including increased expression of cell-cycle regulators, dysfunctional cell cycling, increased DNA damage, and secretion of pro-inflammatory molecules. Sequencing data has uncovered unique clusters in the PMS iNSCs, associated with DNA damage and cell cycling.
Conclusions: Our results highlight a novel DA cellular mechanism in PMS wherein iNSCs and their progeny become dysfunctional and lose their intrinsic cellular resilience. Further characterisation of this model system will uncover how these DA cells intrinsically become dysfunctional and how they affect their microenvironment.

Disclosure
AMN is funded by an ECTRIMS Postdoctoral Research Fellowship Exchange Program (G104956). RBI is funded by a Medical Research Council Doctoral Training Partnership (MRC DTP) award (RG86932) and a Cambridge Trust scholarship. CMW is funded by a National Multiple Sclerosis Society Personal Fellowship (FG-2008-36954). IB, BP, and JW have no conflicts of interest and are funded by the NIA Intramural Research Program. FA is funded by the French Association against Myopathies (AFM)-Telethon. MA is funded by AFM-Telethon, Inserm, Genopole (Chair Fondagen) and the Agence Nationale de la Recherche (ANR-16-CE18 STaHR and ANR20-CE17-0016-01). TL is a consultant for STORM Therapeutics Limited and received reimbursement of expenses from Oxford Nanopore Technologies to speak at sponsored conferences. SP is co-founder and shareholder (>5%) of CITC Ltd.; co-founder and Non-Executive Director (NED) at asitia Therapeutics and iSTEM Therapeutics; and CEO at ReNeuron. This work has received support from the National Multiple Sclerosis Society (USA; grant RG-1802-30200 to SP), the Italian Multiple Sclerosis Association (AISM, grant 2018/R/14 to SP), the United States Department of Defense (DoD) Congressionally Directed Medical Research Programs (CDMRP) (grant MS-140019 to SP), and the Bascule Charitable Trust (RG 75149 and RG 98181 to SP).