ECTRIMS 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

S. Simpson-Yap[1,2], A. Pirmani[3,4], E. De Brouwer[4], L. Geys[3], T. Parciak[5,3], A. Helme[6], N. Rijke[6], T. Kalincik[7,2], J. Hillert[8], Y. Moreau[4], G. Edan[9], T. Spelman[8], R. McBurney[10], H. Schmidt[10], A. Bergmann[11], S. Braune[11], A. Stahmann[12], A. Salter[13], B. Bebo[14], A. van der Walt[15], H. Butzkueven[15], J.I. Rojas[16], I. van der Mei[17], G. Sciascia do Olival[18], M. Magyari[19], R. Alonso[20,21], R. Nicholas[22,23], A. Chertcoff[24,21], A. Zabalza[25], G. Arrambide[25], S. Sharmin[2], A. Descamps[26], L. Costers[26], R. Dobson[27], A. Miller[28], P. Rodrigues[29], G. Comi[30], L. Peeters[3]

[1]University of Melbourne, Neuroepidemiology Unit, Melbourne School of Population & Global Health, Carlton, Australia, [2]Royal Melbourne Hospital, CORe (Clinical Outcomes Research Unit), Melbourne, Australia, [3]Hasselt University, Biomedical Research Institute - Data Science Institute, Diepenbeek, Belgium, [4]KU Leuven, ESAT-STADIUS, Leuven, Belgium, [5]University Medical Center Göttingen, Department of Medical Informatics, Göttingen, Germany, [6]MS International Federation, London, United Kingdom, [7]Royal Melbourne Hospital, Melbourne MS Center, Department of Neurology, Melbourne, Australia, [8]Swedish MS Registry, Department of Clinical Neuroscience, Stockholm, Sweden, [9]CHU Pontchaillou, Department of Neurology , Rennes, France, [10]Accelerated Cure Project for MS, iConquerMS People-Powered Research Network, Waltham, United States, [11]NeuroTransData, NeuroTransData study group, Neuburg, Germany, [12]MS Forschungs- und Projektentwicklungs-gGmbH, MS - Register by the National MS Society, Hannover, Germany, [13]Washington University in St Louis, COViMS, Division of Biostatistics, St Louis, United States, [14]National Multiple Sclerosis Society (USA), COViMS, Portland, United States, [15]Monash University, Australian and New Zealand Cohort, Department of Neuroscience, Central Clinical School, Melbourne, Australia, [16]Hospital Universitario de CEMIC, RELACOEM, Neurology Department, Buenos Aires, Argentina, [17]University of Tasmania, The Australian MS longitudinal study (AMSLS), Menzies Institute for Medical Research, Hobart, Australia, [18]ABEM - Brazilian MS Patients Association, Indianópolis, Brazil, [19]University Hospital Rigshospitalet, Copenhagen, The Danish Multiple Sclerosis Registry, Department of Neurology, Glostrup, Denmark, [20]Ramos Mejia Hospital, RELACOEM, Multiple Sclerosis University Center, Buenos Aires, Argentina, [21]Esclerosis Múltiple Argentina (EMA), Buenos Aires, Argentina, [22]UK MS Register, Swansea, United Kingdom, [23]Imperial College London, London, United Kingdom, [24]Hospital Británico de Buenos Aires, MS and Demyelinating Diseases, Buenos Aires, Argentina, [25]Vall d'Hebron Hospital Universitari, Centre d'Esclerosi Múltiple de Catalunya, (Cemcat), Vall d'Hebron Institut de Recerca, Barcelona, Spain, [26]icometrix, Leuven, Belgium, [27]Queen Mary University London, OPTIMISE:MS, Preventive Neurology Unit, London, United Kingdom, [28]Imperial College London, Department of Brain Sciences, London, United Kingdom, [29]QMENTA Inc., Boston, United States, [30]Università Vita Salute san Raffaele, Casa di Cura del Policlinico, Milan, Italy

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 dataset of people with MS who have suspected or confirmed COVID-19 confirms previous findings that male sex, older age, progressive

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MS, higher disability, the use of anti-CD20 medication (ocrelizumab and rituximab) are associated with worse COVID-19 outcomes.

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Effect of SARS-CoV-2 mRNA vaccination in multiple sclerosis patients treated with disease modifying therapies

M.P. Sormani[1,2], M. Inglese[2,3], I. Schiavetti[1], L. Carmisciano[1], A. Laroni[2], C. Lapucci[2], G. Da Rin[4], C. Serrati[5], I. Gandoglia[6], T. Tassinari[7], G. Perego[8], G. Brichetto[9], P. Gazzola[10], A. Mannironi[11], M.L. Stromillo[12], C. Cordioli[13], D. Landi[14], M. Clerico[15], E. Signoriello[16], J. Frau[17], M.T. Ferrò[18], A. Di Sapio[19], L. Pasquali[20], M. Ulivelli[21], F. Marinelli[22], G. Callari[23], R. Iodice[24], G. Liberatore[25], F. Caleri[26], A.M. Repice[27], S. Cordera[28], M.A. Battaglia[29,30], M. Salvetti[31,32], D. Franciotta[33], A. Uccelli[2,3], CovaXiMS Study Group
[1]University of Genoa, Department of Health Sciences, Genova, Italy, [2]Ospedale Policlinico San Martino IRCCS, Genova, Italy, [3]University of Genoa, Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health 15 (DINOGMI) and Center of Excellence for Biomedical Research (CEBR), Genova, Italy, [4]IRCCS Ospedale Policlinico San Martino, Laboratory Medicine, Genova, Italy, [5]Imperia Hospital, Department of Neurology, Imperia, Italy, [6]Neurology Unit, Galliera Hospital, Genova, Italy, [7]Ospedale Santa Corona Pietra Ligure, S.C. Neurologia, Savona, Italy, [8]ASL 4 Chiavarese, S.C. Neurologia, Chiavari (GE), Italy, [9]AISM Rehabilitation Center, Genova, Italy, [10]Centro Sclerosi Multipla S.C. Neurologia Asl 3 Genovese, Genova, Italy, [11]Sant'Andrea Hospital, Department of Neurology, La Spezia, Italy, [12]Università degli Studi di Siena, Clinica Neurologica e Malattie Neurometaboliche, Siena, Italy, [13]ASST Spedali Civili di Brescia, Centro Sclerosi Multipla, Brescia, Italy, [14]Tor Vergata University and Hospital, Multiple Sclerosis Clinical and Research Unit, Department of Systems Medicine,, Roma, Italy, [15]Università di Torino, Dipartimento di Scienze Cliniche e Biologiche, Torino, Italy, [16]Università della Campania Luigi Vanvitelli, Centro Sclerosi Multipla, II Clinica Neurologica, Napoli, Italy, [17]Ospedale Binaghi Cagliari - ATS Sardegna, Università di Cagliari, Centro Sclerosi Multipla, Cagliari, Italy, [18]ASST Crema, Neuroimmunology, Center for Multiple Sclerosis, Cerobrovascular Department, Neurological Unit, Crema, Italy, [19]Regina Montis Regalis Hospital, Department of Neurology, Mondovì, Italy, [20]University of Pisa, Department of Clinical and Experimental Medicine, Neurology Unit, Pisa, Italy, [21]University of Siena, Department of Medicine, Surgery and Neuroscience, Siena, Italy, [22]Fabrizio Spaziani Hospital, Multiple Sclerosis Center, Frosinone, Italy, [23]Fondazione Istituto G. Giglio, Cefalù, UOC Neurologia e Centro SM, Cefalù, Italy, [24]Università Federico II di Napoli, Clinica Neurologica, DSNRO, Napoli, Italy, [25]IRCCS Humanitas Research Hospital, Neuromuscular and Neuroimmunology Service, Rozzano, Italy, [26]F. Tappeiner Hospital Meran, MS Center, Department of Neurology, Bolzano, Italy, [27]Careggi University Hospital, Department of Neurology, Florence, Italy, [28]Ospedale Regionale Aosta, Department of Neurology, Aosta, Italy, [29]Italian Multiple Sclerosis Foundation, Research Department, Genova, Italy, [30]University of Siena, Department of Life Sciences, Siena, Italy, [31]Sapienza University of Rome, Centre for Experimental Neurological Therapies (CENTERS), Department of Neurosciences, Mental Health and Sensory Organs, Roma, Italy, [32]IRCCS Istituto Neurologico Mediterraneo Neuromed, Pozzilli, Italy, [33]IRCCS Ospedale Policlinico San Martino, Autoimmunology Laboratory, Genova, Italy

Introduction: In patients with Multiple Sclerosis (pwMS) disease-modifying therapies (DMTs) are known to affect immune response to antigens and possibly to SARS-CoV2 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, 25 (3.2%) on cladribine and 404 (51.7%) on other DMTs. 677 patients (86.8%) had detectable post-vaccination SARS-CoV-2 antibodies. At multivariate analysis, the antibody levels of patients on ocrelizumab (178-fold decrease, $p<0.001$), fingolimod (26-fold decrease, $p<0.001$) and rituximab (17-fold decrease, $p<0.001$) were significantly reduced as compared to untreated patients. Vaccination with mRNA-1273 resulted in a systematically 3.5-fold higher antibody level than with the BNT162b2 vaccine ($p<0.001$).
Interpretation: In pwMS, anti-CD20 treatment and fingolimod led to a reduced humoral response to mRNA-based SARS-CoV-2

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.

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ECTRIMS-EAN European consensus on vaccination in patients with multiple sclerosis: improving immunization strategies in the era of highly active immunotherapeutic drugs

S. Otero-Romero[1,2], C. Lebrun-Frénay[3], S. Reyes[4,5,6], M.P. Amato[7,8], M. Campins[2], M.F. Farez[9], M. Filippi[10,11,12], B. Hemmer[13], Y. Hacohen, R. Juuti[14], M. Melinda[15], C. Oreja-Guevara[16], A. Siva[17], S. Vukusic[18], M. Tintoré[19]

[1]Multiple Sclerosis Centre of Catalonia (Cemcat), Hospital Universitari Vall d’Hebron & VHIR, Universitat Autònoma de Barcelona, Department of Epidemiology and Preventive Medicine, Barcelona, Spain, [2]Hospital Universitari Vall d’Hebron & VHIR, Universitat Autònoma de Barcelona, Department of Epidemiology and Preventive Medicine, Barcelona, Spain, [3]Université´ Nice Côte d’Azur UR2CA-URRIS, CRCSEP Côte d’Azur, CHU de Nice Pasteur2, Nice, France, [4]Fundación Santa Fe de Bogotá, Bogotá, Colombia, [5]Universidad de los Andes, School of Medicine, Bogotá, Colombia, [6]Queen Mary University of London, Blizard Institute, Barts and The London School of Medicine and Dentistry, London, United Kingdom, [7]University of Florence, Department NEUROFARBA, Florence, Italy, [8]Fondazione Don Carlo Gnocchi, IRCCS, Florence, Italy, [9]Centro para la Investigación de Enfermedades Neuroinmunológicas, Departamento de Neurología, FLENI, Buenos Aires, Argentina, [10]IRCCS San Raffaele Scientific Institute, Neuroimaging Research Unit, Division of Neuroscience, Milan, Italy, [11]IRCCS San Raffaele Scientific Institute, Neurology Unit, Neurorehabilitation Unit, and Neurophysiology Service, Milan, Italy, [12]Vita-Salute San Raffaele University, Milan, Italy, [13]School of Medicine, Technical University of Munich, Department of Neurology, Klinikum rechts der Isar, Munich, Germany, [14]Multiple Sclerosis International Federation, Patient representative, London, United Kingdom, [15]Rigshospitalet and University of Copenhagen, Department of Neurology, Danish Multiple Sclerosis Center and the Danish Multiple Sclerosis Registry, Copenhagen, Denmark, [16]Hospital Clínico San Carlos, IdISSC, Departamento de Medicina, Universidad Complutense, Department of Neurology, Madrid, Spain, [17]Istanbul University Cerrahpasa School of Medicine, Department of Neurology, Istanbul, Turkey, [18]Hôpital Neurologique Pierre Wertheimer, Hospices Civils de Lyon, Service de neurologie, Sclérose en plaques, Pathologies de la myéline et neuro-inflammation, and Centre de Référence des Maladies Inflammatoires Rares du Cerveau et de la Moelle, Lyon/Bron, France, [19]Multiple Sclerosis Centre of Catalonia (Cemcat), Hospital Universitari Vall d’Hebron & VHIR, Universitat Autònoma de Barcelona, Department of Neurology/ Neuroimmunology, Barcelona, Spain

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.

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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

G. Bsteh[1], H. Hegen[2], G. Traxler[3], S. Dürauer[4], F. Leutmezer[1], F. Di Pauli[2], P. Rommer[1], G. Zulehner[1], F. Deisenhammer[2], M. Guger[3], R. Höftberger[4], T. Berger[1]
[1]Medical University of Vienna, Neurology, Vienna, Austria, [2]Medical University of Innsbruck, Neurology, Innsbruck, Austria, [3]Med Campus III Kepler University Hospital GmbH Linz, Neurology 2, Linz, Austria, [4]Medical University of Vienna, Division of Neuropathology and Neurochemistry, Department of Neurology, Vienna, Austria

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 and safety of SARS-CoV-2 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 (sphingosine 1 receptor modulators [S1PM], antiCD20 monoclonal antibodies [CD20mAb], cladribine) 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 S1PM (75%). Detailed analyses reporting antibody titer levels and role of vaccine type, as well as influence of baseline lymphocyte count, time interval from last DMT dosing, vaccine efficacy and safety parameters 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.

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Early predictors of disability in paediatric multiple sclerosis: evidence from a multi-national cohort

S. Sharmin[1], C. Malpas[1,2], I. Roos[1,2], I. Diouf[1], R. Alroughani[3], S. Ozakbas[4], G. Izquierdo[5], S. Eichau[5], D. Horakova[6,7], E.K. Havrdova[6,7], F. Patti[8], M. Terzi[9], C. Boz[10], B. Yamout[11], S.J Khoury[11], M. Onofrj[12], A. Lugaresi[13,14], A. Altintas[15], A. Prat[16], M. Girard[16], P. Duquette[16], M.J. Sa[17], D. Spitaleri[18], Y. Sidhom[19], R. Gouider[19], A. Soysal[20], R. Turkoglu[21], M.P. Amato[22], Y. Fragoso[23], T. Kalincik[1,2]

[1]University of Melbourne, Melbourne, Australia, [2]Royal Melbourne Hospital, Melbourne, Australia, [3]Amiri Hospital, Sharq, Kuwait, [4]Dokuz Eylul University, Konak/Izmir, Turkey, [5]Hospital Universitario Virgen Macarena, Sevilla, Spain, [6]Charles University, Prague, Czech Republic, [7]General University Hospital, Prague, Czech Republic, [8]University of Catania, Catania, Italy, [9]19 Mayis University, Samsun, Turkey, [10]KTU Medical Faculty Farabi Hospital, Trabzon, Turkey, [11]American University of Beirut Medical Center, Beirut, Lebanon, [12]University G. d'Annunzio, Chieti, Italy, [13]IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy, [14]Università di Bologna, Bologna, Italy, [15]Koc University, Istanbul, Turkey, [16]CHUM MS Center and Universite de Montreal, Montreal, Canada, [17]Centro Hospitalar Universitario de Sao Joao, Porto, Portugal, [18]Azienda Ospedaliera di Rilievo Nazionale San Giuseppe Moscati Avellino, Avellino, Italy, [19]Razi Hospital, Manouba, Tunisia, [20]Bakirkoy Education and Research Hospital for Psychiatric and Neurological Diseases, Istanbul, Turkey, [21]Haydarpasa Numune Training and Research Hospital, Istanbul, Turkey, [22]University of Florence, Florence, Italy, [23]Universidade Metropolitana de Santos, Santos, Brazil

Introduction: Early recognition of markers of faster disability worsening 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 duration) included: age at symptoms onset, complete recovery from first relapse, 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

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[11C]flumazenil positron emission tomography in multiple sclerosis: model validation and clinical applicability in cognitive impairment

M. Huiskamp[1], B.N. van Berckel[2], R. Boellaard[2], L.R. de Ruiter[3], J.J. Geurts[4], M.M. Yaqub[2], H.E. Hulst[4]
[1]Amsterdam UMC, Anatomy and neurosciences, MS Center Amsterdam, Amsterdam Neuroscience, Vrije Universiteit Amsterdam, Amsterdam, Netherlands, [2]Amsterdam UMC, Radiology and Nuclear Medicine, Amsterdam, Netherlands, [3]Amsterdam UMC, Neurology, Amsterdam, Netherlands, [4]Amsterdam UMC, Anatomy and Neurosciences, MS Center Amsterdam, Amsterdam Neuroscience, Vrije Universiteit Amsterdam, Amsterdam, Netherlands

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 [^{11}C]flumazenil Positron Emission Tomography ([^{11}C]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 [^{11}C]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 [^{11}C]

FMZ was administered and discrete and continuous arterial blood was withdrawn 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 (K_1) and volume of distribution (V_T) were determined for 7 brain areas relevant for cognition: superior frontal, fusiform and parahippocampal gyri, hippocampus, thalamus and anterior and posterior cingulate cortex. Finally, neuropsychological testing (adjusted BRB-N) was used to classify patients as CI (when scoring $z \leqslant -1.5$ on $\geqslant 2/9$ 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 V_T was highly correlated among both models (Pearson's r=.98), making the simpler 1T2K_VB the optimal model. In MS, K_1 was lower than in HCs (P=.02), while V_T was higher (P=.002). When comparing CI (N=10) and CP (N=5) patients to HCs, CI patients had lower K_1 values than HCs (P=.001) and CP patients (P=.006). V_T values were higher in both patient groups compared to controls (P=.007).

Conclusion: The 1T2K_VB was the preferred model for analysis of [^{11}C]FMZ data in MS. K_1 and V_T 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.

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Cellular immune profiling pre- and post-aCD20 therapy points to differential effects on CD4$^+$ and CD8$^+$ T cells and implicates CD20-expressing CD8$^+$ T cells in MS disease activity

K. Shinoda[1,2], R. Li[1,2], A. Rezk[1,2], I. Mexhitaj[1,2], K.R. Patterson[1,2], M. Kakara[1,2], L. Zuroff[1,2], J.L. Bennett[3], H.-C. von Büdingen[4], R. Carruthers[5], K.R. Edwards[6], R. Fallis[7], P.S. Giacomini[8], B. Greenberg[9], D.A. Hafler[10], C. Ionete[11], U.W. Kaunzner[12], C.B. Lock[13], E.E. Longbrake[14], G. Pardo[15], F. Piehl[16,17,18], M. Weber[19,20], T. Ziemssen[21], J.M. Gelfand[22], A.H. Cross[23], B. Cameron[24], B. Musch[24], R. Winger[24], X. Jia[24], C. Harp[24], A. Herman[24], A. Bar-Or[1,2,25]

[1]University of Pennsylvania, Department of Neurology, Perelman School of Medicine, Philadelphia, United States, [2]University of Pennsylvania, Center for Neuroinflammation and Experimental Therapeutics, Perelman School of Medicine, Philadelphia, United States, [3]University of Colorado School of Medicine, Departments of Neurology and Ophthalmology, Programs in Neuroscience and Immunology, Aurora, United States, [4]F. Hoffmann-La Roche Ltd., Basel, Switzerland, [5]University of British Columbia, Vancouver, Canada, [6]MS Center of Northeastern New York, Comprehensive MS Care Center Affiliated with the National MS Society, Latham, United States, [7]Ohio State University Medical Center, Department of Neurology, Columbus, United States, [8]McGill University, Department of Neurology and Neurosurgery, Montreal Neurological Institute, Montreal, Canada, [9]UT Southwestern Medical Center, Dallas, United States, [10]Department of Neurology, Yale School of Medicine, New Haven, United States, [11]University of Massachusetts Medical School, Department of Neurology, Worcester, United States, [12]Weill Cornell Medicine, Judith Jaffe Multiple Sclerosis Center, New York, United States, [13]Stanford University, Department of Neurology and Neurological Sciences, Palo Alto, United States, [14]Yale University, Department of Neurology, New Haven, United States, [15]Oklahoma Medical Research Foundation, Multiple Sclerosis Center of Excellence, Oklahoma City, United States, [16]Karolinska Institute, Department of Clinical Neuroscience, Stockholm, Sweden, [17]Karolinska University Hospital, Department of Neurology, Stockholm, Sweden, [18]Karolinska Institute, Neuroimmunology Unit, Center for Molecular Medicine, Karolinska University Hospital, Stockholm, Sweden, [19]University Medical Center, Institute of Neuropathology, Göttingen, Germany, [20]University Medical Centerunit, Department of Neurology, Göttingen, Germany, [21]Dresden University of Technology, MS Center Dresden, Center of Clinical Neuroscience, Neurological Clinic, University Hospital Carl Gustav Carus, Dresden, Germany, [22]University of California, Multiple Sclerosis Center, Weill Institute for Neurosciences, San Francisco, United States, [23]Washington University School of Medicine, Department of Neurology, Saint Louis, United States, [24]Genentech, Inc., San Francisco, United States, [25]University of Pennsylvania, Children's Hospital of Philadelphia, Philadelphia, United States

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 pre-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 $CD8^+$ 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.

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Neuregulin-1 facilitates remyelination by promoting the reparative properties of macrophages and microglia in animal models of multiple sclerosis

H. Kataria[1], S.M. Ziaee[1], S.M. Hosseini[1], G. McLeod[1], K. Akbari-Kelachayeh[1], S. Karimi-Abdolrezaee[1]
[1]University of Manitoba, Department of Physiology and Pathophysiology, Spinal Cord Research Centre, Rady Faculty of Health Sciences, Winnipeg, Canada

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 it effects 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.

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Decline of neural stem cell resilience in multiple sclerosis

A. Nicaise[1], R.-B. Ionescu[1], C. Willis[1], J. Whitten[2], B. Park[2], T. Leonardi[3], M. Lancaster[4], F. Amor[5], M. Amendola[5], V. Fossati[6], S. Rizzi[7], F. Edenhofer[7], I. Beerman[2], S. Pluchino[1]
[1]University of Cambridge, Cambridge, United Kingdom, [2]National Institute on Aging, Baltimore, United States, [3]Italian Institute of Technology, Milan, Italy, [4]MRC Laboratory of Molecular Biology, Cambridge, United Kingdom, [5]Genethon, Inserm, Evry, France, [6]The New York Stem Cell Foundation, New York, United States, [7]Leopold-Franzens-University Innsbruck, Innsbruck, Austria

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 behaviours, 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.

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