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Introduction: A short term course of cladribine has a prolonged effect on the clinical course of MS.The exact mechanism of this phenomenon is unknown.
Objectives: To examine the effect of cladribine on T regulatory cells (Treg) using markers of activation and chemokine receptors and comparing this to the effect on B cell subsets.
Methods: Peripheral blood was collected from healthy donors and MS patients prior to cladribine therapy and then at 1, 6, 12, 24 and 30 months post therapy. Peripheral blood mononuclear cells (PBMC) were isolated from whole blood using Ficoll-Hypaque density gradient centrifugation. Fresh PBMC ($1x10^6$) were stained with panels of antibodies for activated and naïve Treg (CD4, CD127, CD25, Foxp3, CD45RA, CXCR3, CCR6, CCR4) and B cell subset (CD45, CD19, CD27, CD21, IgD, IgM, CD38, CD24) identification. For Treg staining, cells were first stained with chemokine receptors for 15 minutes at room temperature in the dark before staining for other surface markers CD4, CD25, CD127 and CD45RA, before staining for Foxp3. For B cells, cells were stained with the full panel of antibodies for 30min.Phenotypic analysis was performed on stained PBMC using a FACSCanto II flow cytometer (BD Biosciences) and FACS DIVA 8.0 software. The data was analysed using Flojo software to examine changes in naïve and activated Treg and B cell subsets. Ratios and absolute numbers including the ratio of Treg to B cell subsets were calculated. Data was analysed using GraphPad Prism and significance was set as $p<0.05$.
Results: The most dramatic effects were the early increases in the ratios of Treg to all B cells in patients treated with cladribine compared with HD. However this effect dissipated after 3 months. The more persistent effects were seen in an increased ratio of Treg to memory B cells, marginal zone B cells, transitionalB cells, and switched and unswitched memory B cells. There was a significantly higher ratio of Treg to memory B cells at 3mth (2.62 vs 0.36, $p<0.05$), 12mth (1.993 vs 0.31, $p<0.001$) which stayed higher until 30-mth post cladribine. As absolute numbers (x 10^9/L) also, 3mth (18.73 vs 1.038, $p<0.001$).
Conclusion: The data suggests that an increased ratio of activated Treg to activated B cells may contribute to the prolonged effect of cladribine therapy.

Disclosure
This work was partially supported by an investigator-initiated study grant by Merck Healthcare Pty. Ltd., Macquarie Park, Australia, an affiliate of Merck (CrossRef Funder ID: 10.13039/100009945)

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Comparative effectiveness of autologous haematopoietic stem cell transplantation with immune reconstitution therapies in relapsing-remitting MS

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Intro: Chemotherapy with autologous hematopoietic stem cell transplantation (AHSCT) has been increasingly used in highly active multiple sclerosis (MS). Information about its comparative effectiveness relative to immune reconstitution therapies is lacking.

Aim: This study emulated pairwise trials of comparative effectiveness of AHSCT vs. alemtuzumab, cladribine tablets and mitoxantrone (an older, broadly immunosuppressive therapy).

Methods: Patients with relapsing-remitting MS from 6 AHSCT MS centres in Ottawa, Uppsala, Sheffield, Bergen, Sydney and Melbourne were combined with patients from MSBase. Included patients were treated with AHSCT or one of the study therapies and had sufficient information recorded before and after the start of the treatments (baseline). Groups were matched on a propensity score derived from sex, age, disability score (EDSS), number of relapses 12 and 24 months before baseline, time from MS onset, the most effective prior therapy and country. The pairwise-censored groups were compared on annualised relapse rates (ARR), hazards of relapses and 6-month confirmed EDSS worsening and improvement.

Results: The matched patients had high mean disease activity (>0.9 relapses in the prior year), mean EDSS 3-4.5, and matched follow-up of 2-3 years.Alemtuzumab (n=284) and AHSCT (n=122) were associated with similar ARR (mean±SD 0.13±0.31 vs. 0.11±0.35), risk of relapses (hazard ratio 0.79, 95%CI 0.46-1.37), similar risk of EDSS worsening (hazard ratio 0.82, 95%CI 0.33-2.03) and EDSS improvement (hazard ratio 1.07, 95%CI 0.74-1.57). Cladribine (173) and AHSCT (65) were associated with similar ARR (0.16±0.48 vs. 0.10±0.38), risk of relapses (0.63, 0.22-1.77), EDSS worsening (0.51, 0.08-3.14) and EDSS improvement (1.24, 0.44-3.78). Compared to Mitoxantrone (91), AHSCT (30) was associated with lower ARR (0.35±0.74 vs. 0.17±0.57) and a corresponding trend for the risk of relapses (0.48, 0.18-1.28). We did not find evidence for differences in EDSS worsening (0.49, 0.16-1.54) and EDSS improvement (1.19, 0.24-5.88).

Conclusion: In this limited cohort with highly active MS and moderate disability, the clinical effectiveness of AHSCT was comparable to two immune reconstitution therapies – alemtuzumab and cladribine. There was evidence for superior prevention of relapses by AHSCT than by mitoxantrone, but no evidence for difference in disability outcomes. Further comparison of AHSCT to these therapies in cohorts and trials over extended time is warranted.

Disclosure

Tomas Kalincik served on scientific advisory boards for BMS, Roche, Janssen, 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, Eisai, Novartis, Biogen, Sanofi-Genzyme, Teva, BioCSL and Merck and received research or educational event support from Biogen, Novartis, Genzyme, Roche, Celgene and Merck.

Sifat Sharmin has nothing to disclose.

Izanne Roos served on scientific advisory boards/steering committees for Novartis and Merck and received conference travel support and/or speaker honoraria from Roche, Novartis, Biogen, Teva, Sanofi-Genzyme and Merck.

Mark Freedman has nothing to disclose.

Harold Atkins has nothing to disclose.

Joachim Burman has nothing to disclose.

Ian Sutton has nothing to disclose.

Barbara Withers did not declare any disclosures.

Jennifer Massey served on scientific advisory board for Roche, received conference travel support and/or speaker honoraria from Novartis, Biogen, Roche and Merck.

Richard Macdonell received compensation for traveling, conference fees and consulting fees from Merck, Teva, Sanofi Genzyme, Biogen Idec, Novartis, Roche, BMS, Celgene.

Andrew Grigg has nothing to disclose.

Oivind Torkildsen received speaker honoraria from and served on scientific advisory boards for Biogen, Sanofi-Aventis, Merck and Novartis.

Lars Bo received speaker honoraria from Novartis, and consultant fees from Viatris.

Anne Kristin Lehmann did not declare any disclosures.

Dana Horakova received speaker honoraria and consulting fees from Biogen, Merck, Teva, Roche, Sanofi Genzyme, and Novartis, as well as support for research activities from Biogen andCzech Minsitry of Education [project Progres Q27/LF1].

Eva Kubala Havrdova received honoraria/research support from Biogen, Merck Serono, Novars, Roche, and Teva; has been member of advisory boards for Actelion, Biogen, Celgene, Merck Serono, Novars, and Sanofi Genzyme.

Eva Krasulova has nothing to disclose.

Marek Trneny received honoraria from Janssen, Gilead Sciences, Bristol-Myers Squibb, Takeda, Amgen, Abbvie, Roche, MorphoSys, Novartis, served as an advisor to Takeda, Bristol-Myers Squibb, Incyte, Abbvie, Amgen, Roche, Gilead Sciences, Janssen, MorphoSys, Novartis, and received conference travel support from Gilead Sciences, Takeda, Bristol-Myers Squibb, Roche, Janssen and Abbvie.

Tomas Kozak has nothing to disclose.

Anneke van der Walt served on advisory boards and receives unrestricted research grants from Novartis, Biogen, Merck and Roche She has received speaker's honoraria and travel support from Novartis, Roche, and Merck. She receives grant support from the National Health and Medical Research Council of Australia and MS Research Australia.

Helmut Butzkueven received institutional (Monash University) funding from Biogen, F. Hoffmann-La Roche Ltd, Merck, Alexion, CSL, and Novartis; has carried out contracted research

for Novartis, Merck, F. Hoffmann-La Roche Ltd and Biogen; has taken part in speakers' bureaus for Biogen, Genzyme, UCB, Novartis, F. Hoffmann-La Roche Ltd and Merck; has received personal compensation from Oxford Health Policy Forum for the Brain Health Steering Committee.
Bart Van Wijmeersch received research and rravel grants, honoraria for MS-Expert advisor and Speaker fees from Bayer-Schering, Biogen, Sanofi Genzyme, Merck, Novartis, Roche and Teva.
Pamela McCombe received speakers fees and travel grants from Novartis, Biogen, T'évalua, Sanofi
Katherine Buzzard received honoraria and consulting fees from Biogen, Teva, Novartis, Genzyme-Sanofi, Roche, Merck, CSL and Grifols.
Olga Skibina has nothing to disclose.
Jeannette Lechner-Scott travel compensation from Novartis, Biogen, Roche and Merck. Her institution receives the honoraria for talks and advisory board commitment as well as research grants from Biogen, Merck, Roche, TEVA and Novartis.
Barbara Willekens Barbara Willekens received honoraria for acting as a member of Scientific Advisory Boards for Almirall, Biogen, Celgene/BMS, Merck Serono, Novartis, Roche, Sanofi-Genzyme and speaker honoraria and travel support from Biogen, Merck Serono, Novartis, Roche, Sanofi-Genzyme; research and/or patient support grants from Roche, Biogen, Merck-Serono, Sanofi-Genzyme. Honoraria and grants were paid to UZA/UZA Foundation.
Michael Barnett served on scientific advisory boards for Biogen, Novartis and Genzyme and has received conference travel support from Biogen and Novartis. He serves on steering committees for trials conducted by Novartis. His institution has received research support from Biogen, Merck and Novartis.
Pamela McCombe received honoraria and consulting fees from Novartis, Bayer Schering andSanofi and travel grants from Novartis, Biogen and Bayer Schering.
Elisabetta Cartechini has nothing to disclose.
Guillermo Izquierdo received speaking honoraria from Biogen, Novartis, Sanofi, Merck, Roche, Almirall and Teva.
Sara Eichau received speaker honoraria and consultant fees from Biogen Idec, Novartis, Merck, Bayer, Sanofi Genzyme, Roche and Teva.
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.
Suzanne Hodgkinson received honoraria and consulting fees from Novartis, Bayer Schering and Sanofi, and travel grants from Novartis, Biogen Idec and Bayer Schering.
Julie Prevost accepted travel compensation from Novartis, Biogen, Genzyme, Teva, and speaking honoraria from Biogen, Novartis, Genzyme and Teva.
Marco Onofrj has nothing to disclose.
Alessandra Lugaresi has received personal compensation for consulting, serving on a scientific advisory board, speaking or other activities from Biogen, Merck Serono, Mylan, Novartis, Roche, Sanofi/Genzyme, Teva. Her institutions have receved research grants from Novartis [last 4 yrs].
Raed Alroughani received honoraria as a speaker and for serving on scientific advisory boards from Bayer, Biogen, GSK, Merck, Novartis, Roche and Sanofi-Genzyme.
Ernest Butler has nothing to disclose.
Alexandre Prat has nothing to disclose.
Marc Girard received consulting fees from Teva Canada Innovation, Biogen, Novartis and Genzyme Sanofi; lecture payments from Teva Canada Innovation, Novartis and EMD .He has also received a research grant from Canadian Institutes of Health Research.
Pierre Duquette served on editorial boards and has been supported to attend meetings by EMD, Biogen, Novartis, Genzyme, and TEVA Neuroscience. He holds grants from the CIHR and the MS Society of Canada and has received funding for investigator-initiated trials from Biogen, Novartis, and Genzyme.
Pierre Grammond has served in advisory boards for Novartis, EMD Serono, Roche, Biogen idec, Sanofi Genzyme, Pendopharm and has received grant support from Genzyme and Roche, has received research grants for his institution from Biogen idec, Sanofi Genzyme, EMD Serono.
Francois Grand'Maison received honoraria or research funding from Biogen, Genzyme, Novartis, Teva Neurosciences, Mitsubishi and ONO Pharmaceuticals.
Guy Laureys received travel and/or consultancy compensation from Sanofi-Genzyme, Roche, Teva, Merck, Novartis, Celgene, Biogen.
Liesbeth Van Hijfte has nothing to disclose.
Davide Maimone received speaker honoraria for Advisory Board and travel grants from Almirall, Biogen, Merck, Novartis, Roche, Sanofi-Genzyme, and Teva.
Basil Sharrack has nothing to disclose.
John Snowden declares honoraria for educational events from Jazz, Gilead, Janssen, for advisory board membership from Medac, and for trial IDMC membership from Kiadis Pharma.

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Is disease-modifying therapy use in the multiple sclerosis a risk factor during the COVID-19 pandemic? A large cohort study

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Introduction: The role of ongoing disease-modifying therapy (DMT) in coronavirus disease 2019 (Covid-19) morbidity and mortality in people with multiple sclerosis (MS, pwMS) is uncertain. The MS International Federation recommends that pwMS continue their medication.
Objectives: To investigate the relationship between DMT used in MS patients and the risk of Covid-19 infection.
Aims: The MS cohort of 3402 people followed for Covid-19 infection was included in this longitudinal cohort study. The whole MS cohort was interviewed at least once for information about Covid-19, by text message, or by phone, during which 487 pwMS were determined with Covid-19 infection. A semi-structured interview,