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UPDATED RESULTS OF THE COVID-19 IN MS GLOBAL DATA SHARING INITIATIVE: ANTI-CD20 DMTs DELETERIOUS FOR COVID-19 SEVERITY BUT INTERFERONS NOT PROTECTIVE AMONG PEOPLE WITH MS

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10.1136/bmjno-2022-ANZAN.25

Objectives Some disease-modifying therapies (DMTs) have been associated with COVID-19 severity in people with MS. Comprehensive exploration of these relationships in large international samples is needed.

Methods Clinician-reported demographic/clinical data from 27 countries were aggregated into a dataset of 5,648 patients with suspected/confirmed COVID-19. COVID-19 severity outcomes (hospitalisation, admission to ICU, requiring artificial ventilation, death) assessed using multilevel mixed-effect ordered probit and logistic regression, adjusted for age, sex, disability, and MS phenotype. DMTs were compared to

glatiramer acetate, dimethyl fumarate, pooled other DMTs, and natalizumab.

Results Of 5,648 patients (83.4% confirmed COVID-19) were included. Compared to glatiramer acetate, ocrelizumab and rituximab were associated with higher probability of hospitalisation (4%(95%CI=1–7) & 7%(95%CI=4–11)), ICU/artificial ventilation (2%(95%CI=0–4) & 4%(95%CI=2–6)), and death (1%(95%CI=0–2) & 2%(95%CI=1–4)) [predicted marginal effects]. Untreated patients had 5%(95%CI=2–8), 3%(95%CI=1–5), and 1%(95%CI=0–3) higher probabilities of the three respective levels of COVID-19 severity than glatiramer acetate. Compared to pooled other DMTs and to natalizumab, the associations of ocrelizumab and rituximab with COVID-19 severity were also more pronounced. Evaluation of interferon associations with COVID-19 severity found these only apparent in comparison with the untreated but not vs individual or pooled other DMTs. All associations persisted/enhanced on restriction to confirmed COVID-19.

Conclusions Analysing the largest international real-world dataset of people with MS with suspected/confirmed COVID-19 confirms that the use of anti-CD20 medication (both ocrelizumab and rituximab) are associated with more severe course of COVID-19, while interferon-based DMTs have no intrinsic protective benefit from other treatment.

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COMPARISON OF THE EFFECTIVENESS OF OCRELIZUMAB VS INTERFERON β , FINGOLIMOD AND NATALIZUMAB ON RELAPSES IN RELAPSING-REMITTING MULTIPLE SCLEROSIS

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10.1136/bmjno-2022-ANZAN.26

Objective To compare the effectiveness of ocrelizumab with interferon- β , fingolimod and natalizumab in relapsing-remitting multiple sclerosis (MS).

Method Using the MSBase registry, we identified patients with relapsing-remitting MS treated for ≥ 6 months with ocrelizumab, interferons (interferon β -1a, interferon β -1b subcutaneous or interferon β -1b intramuscular), fingolimod or natalizumab. Patients were matched with propensity score on baseline age, sex, MS duration, EDSS, relapse rate, prior therapy, disease activity, MRI, reason for discontinuation of preceding therapy and country. Annualised relapse rates (ARR) and cumulative hazard of relapses were compared in pairwise-censored groups.

Results 106 patients treated with ocrelizumab were matched with 209 patients on interferon therapies. Over a pairwise-censored mean follow-up of 1.3 years, ocrelizumab was associated with lower relapse rates (ARR 0.08 vs 0.27, $p < 0.001$) and lower risk of relapse (HR 0.30, 95%CI 0.15–0.57) than

interferon- β . 297 patients treated with ocrelizumab were matched with 811 fingolimod-treated patients. Over a pairwise-censored mean follow-up of 1.5 years, ocrelizumab was associated with lower relapse rates (ARR 0.03 vs 0.14, $p < 0.001$) and lower risk of relapse than fingolimod (HR 0.21, 0.13–0.32). 262 ocrelizumab-treated patients were matched with 343 natalizumab treated. Over a pairwise-censored mean follow-up of 1.6 years, ocrelizumab and natalizumab were associated with similar relapse rates (ARR 0.06 vs 0.08, $p = 0.39$) and risk of relapse (HR 0.77, 0.45–1.33).

Conclusions Treatment with ocrelizumab provides superior control of relapses than interferon- β and fingolimod. The effects of ocrelizumab and natalizumab on relapse activity are similar. Further evaluation of the comparative effectiveness of ocrelizumab on disability accumulation is warranted.

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INCOMPLETE RECOVERY FROM ATTACKS IN EARLY RELAPSING-REMITTING MS HERALDS FASTER DISABILITY PROGRESSION IN SECONDARY PROGRESSIVE MS

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10.1136/bmjno-2022-ANZAN.27

Objective To investigate the association between early relapses shortly after relapsing remitting multiple sclerosis (RRMS) onset and disability progression during secondary progressive MS (SPMS).

Methods In this observational cohort study, 4,988 patients from the MSBase registry who reached SPMS, defined by the Lorscheider criteria, were identified. 1220 patients followed within two years from RRMS onset and over at least one year after SPMS conversion, and with an EDSS score of 4 to 5.5 at SPMS conversion, were included. The outcome was the rate of disability progression during SPMS, calculated with linear regression as mean change in multiple sclerosis severity scores (MSSS) over time. Associations between early disease characteristics (especially annualised relapse rate during the first two years of MS and relapse recovery) with the MSSS change were assessed using multivariable linear regression.

Results Of 1220 patients, 67% were female and the median age of MS diagnosis was 40 years. We found no evidence for association of early relapse rate with disability progression ($\beta = -0.014$, 95% CI -0.067 to 0.037, $p = 0.60$). Male sex, a longer RRMS period and a higher EDSS at progression were associated with faster SPMS disability progression. A higher initial MSSS was associated with slower disability progression. Importantly, a higher proportion of early relapses with incomplete recovery was associated with faster disability progression during SPMS ($\beta = 0.12$, 95% CI 0.017 to 0.22, $p = 0.025$).

Conclusion The rate of relapses during early RRMS is not associated with SPMS disability progression, while incomplete recovery of early relapses is associated with faster disability progression.

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EXTENSIVE REMODELLING OF THE LYMPHOCYTE REPERTOIRE AND DELETION OF AUTOACTIVE CLONES FOLLOWING AHST IN MS

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10.1136/bmjno-2022-ANZAN.28

Objectives Autologous haematopoietic stem cell transplantation (AHST) is a vital therapeutic option for aggressive multiple sclerosis (MS). The mechanism by which AHST enables sustained remission beyond lymphopenia remains to be elucidated.

Methods Bio-banked lymphocytes were collected from MS patients enrolled in a phase 2 trial (ACTRN12613000339752), and comparator patients treated with Natalizumab. A multicolour flow cytometry panel was performed on 19 patient samples pre-AHST, 6, 12, 24 and 36 months post-AHST. DNA markers of thymic function were performed in the same cohort, and thymic PET studies in three patients. Fluorescence-activated cell-sorted T cell sub-populations were acquired for mRNA T-cell receptor sequencing in 13 patients.

Results Early proliferation of (effector and terminal effector) memory T-cells is followed by delayed recovery of naive CD4 + lymphocytes. 40.8% (CD4+CD45RO+) and 32.8% (CD8 +CD45RO+) of clones from the pre-transplant repertoire were detected at 6 months, yet only 19% (CD4+; $p < 0.025$) and 13% (CD8+; $p < 0.005$) of pre-transplant clones were detected at 36 months. Diversity of the memory populations declined post-transplant ($p = 0.012$). Recovery of a thymically-derived naive T cell repertoire is ongoing at 36 months, however diversity of the naive populations only increased from baseline in responders, with activity correlated on PET imaging. In HLA-DRB1*15:01-positive patients, public clones are probed as biomarkers of disease. Twelve public CD4+ clones correlate with disease activity, and two display characteristics on GLIPH2 analysis of autoreactivity.

Conclusions AHST induces sustained remission with dynamic changes in clonal T cell repertoire out to 36 months post-transplant, including the deletion of putative auto-reactive clones.

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LATITUDE, UVR AND MULTIPLE SCLEROSIS SEVERITY

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10.1136/bmjno-2022-ANZAN.29