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.

2292 INCOMPLETE RECOVERY FROM ATTACKS IN EARLY RELAPSING-REMITTING MS HERALDS FASTER DISABILITY PROGRESSION IN SECONDARY PROGRESSIVE MS

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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 (β=-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 (β=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.

2314 EXTENSIVE REMODELLING OF THE LYMPHOCYTE REPERTOIRE AND DELETION OF AUTOREACTIVE CLONES FOLLOWING AHSCT IN MS

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Objectives Autologous haematopoietic stem cell transplantation (AHSCT) is a vital therapeutic option for aggressive multiple sclerosis (MS). The mechanism by which AHSCT 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-AHSCT, 6, 12, 24 and 36 months post-AHSCT. 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 naïve T cell repertoire is ongoing at 36 months, however diversity of the naïve 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 AHSCT 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.

2327 LATITUDE, UVR AND MULTIPLE SCLEROSIS SEVERITY

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Objectives This study aimed to investigate the association between latitude of residence, ultraviolet B radiation exposure (UVB) and MS severity.
Methods This observational study used MSBase registry data. Included patients met the 2005 or 2010 McDonald diagnostic criteria for MS and had a minimum dataset recorded in the registry. The latitude of each study centre and cumulative annualized UVB dose at study centre (from NASA's Total Ozone Mapping Spectrometer) at ages 6, 18 and the year of disability assessment were calculated. Disease severity was quantified with MS Severity Score (MSSS). Quadratic regression was used to model associations between latitude, UVB and MSSS.
Results 46,128 patients contributing 453,208 visits and a cumulative follow-up of 351,196 patient-years (70% women, mean age 39.2±12, resident between latitudes 19°35´-56°16´) were included. Latitude showed a non-linear association with MS severity. In latitudes >40°, more severe disease was associated with higher latitudes (β=0.08, 95%CI: 0.04–0.12). This would translate into a mean difference of 1.3 MSSS points between patients living in Madrid and Copenhagen. No such association was observed in latitudes <40° (β=-0.02, 95% CI:-0.06–0.03). The overall disability accrual was faster in those with a lower estimated UVB exposure before the age of 6 (β=- 0.5, 95% CI: -0.6–0.4) and 18 years (β=- 0.6, 95% CI:-0.7–0.4), as well as with lower life-time UVB exposure at the time of disability assessment (β=-1.0, 95%CI:-1.1–0.9).
Conclusion In temperate zones, MS severity is associated with latitude. This association is mainly, but not exclusively, driven by UVB exposure contributing to MS susceptibility and severity.

2414 EFFICACY OF OCRELIZUMAB IN PEOPLE WITH MULTIPLE SCLEROSIS IS MAINTAINED DESPITE HIGH INCIDENCE OF B-CELL REPOPULATION DURING TREATMENT

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Objective Ocrelizumab is a disease modifying therapy (DMT) for multiple sclerosis that depletes CD20+ B lymphocytes. Memory B-cells have been implicated in the pathogenesis of MS and there is emerging evidence suggesting a role for monitoring class-switched memory B (SMB) cells to guide re-dosing of anti-CD20 therapies in other CNS autoimmune conditions. This study aimed to examine B-cell repopulation and efficacy for ocrelizumab in a real-world setting.
Methods Single-centre retrospective observational study of patients with MS who had received ocrelizumab for ≥18 months with pre-infusion lymphocyte subsets and memory B-cell subtypes checked on ≥3 occasions. Repopulation cut-offs were >0.00x10^9/L for CD19+ B-cells and ≥0.0005x10^9/L for CD19+/CD27+/IgM-/IgD- SMB cells.
Results Sixty-three patients met the inclusion criteria. Of these, 25 (40%) had CD19+ B-cell repopulation and 46 (73%) had SMB repopulation at least once during follow-up. Previous DMT exposure (65% of patients) did not affect the incidence of CD19+ B-cell (34% vs 50%, p=0.34) or SMB cell (73% vs 72%, p>0.99) repopulation.

No patient experienced a confirmed relapse. Six patients (9.5%) developed new or enlarging T2 lesions on MRI >6 months after ocrelizumab initiation. The incidence of MRI activity was not influenced by CD19+ B-cell (8.0% vs 10.5%, p>0.99) or SMB cell (4.3% vs 23.5%, p=0.08) repopulation.
Conclusion CD19+ B-cell and SMB cell repopulation between infusions is common in patients treated with ocrelizumab, but this did not increase the risk of relapse or MRI activity in this study. Future studies may potentially delineate an SMB threshold for individualised dosing.

2367 DEVELOPING TOLEROGENIC DENDRITIC CELLS AS IMMUNOTHERAPY FOR MULTIPLE SCLEROSIS

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Objectives In multiple sclerosis (MS), antigen presenting cells including dendritic cells (DCs) present autoantigens to and activate autoreactive lymphocytes. Many current treatments are broadly immunosuppressive. A more targeted and individualised strategy is to re-establish immune tolerance by exposing DCs to tolerogenic stimuli together with cognate autoantigens specific to HLA haplotype. RASGRP2 has been identified as an MS autoantigen in HLA-DRB1*15:01 (DR15)-positive individuals. We aimed to develop tolerogenic DCs as immunotherapy for MS.
Methods CD14+ monocytes isolated from peripheral blood mononuclear cells of people with MS and healthy donors were differentiated to DCs under different conditions and co-cultured with autologous CD4+ T-cells. DC surface molecule expression, myelin phagocytosis and T-cell proliferation were assessed by flow cytometry, and cytokine production by bead-based immunoassay. DNA extracted from blood was used for DR15 genotyping. Antigen presenting cells from different individuals were incubated with a library of synthesised RASGRP2-derived peptides of varying DR15 binding affinities to examine presentation using immunopeptidomic techniques and immune reactivity.
Results DCs treated with dexamethasone developed tolerogenic properties including lower surface MHC-II and co-stimulatory molecule expression, lower pro-inflammatory cytokine production, increased myelin debris phagocytosis and reduced proliferation of co-cultured CD4+ T-cells. We observed HLA-DR15 genotype-dependent differences in co-stimulatory molecule expression and dexamethasone response. RASGRP2 peptides with moderate DR15 binding affinity elicited the greatest

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