Phenome-Wide Examination of Comorbidity Burden and Multiple Sclerosis Disease Severity

**Objective** We assessed the comorbidity burden associated with multiple sclerosis (MS) severity by performing a phenome-wide association study (PheWAS).

**Methods** We conducted a PheWAS in 2 independent cohorts: a discovery (Boston, United States; 1993–2014) and extension cohort (British Columbia, Canada; 1991–2008). We included adults with MS, ≥1 Expanded Disability Status Scale (EDSS) score, and ≥1 International Classification of Diseases (ICD) code other than MS. We calculated the Multiple Sclerosis Severity Score (MSSS) using the EDSS. We mapped ICD codes into PheCodes (phenotypes), using a published system with each PheCode representing a unique medical condition. Association between the MSSS and the presence of each condition was assessed using logistic regression adjusted for covariates.

**Results** The discovery and extension cohorts included 3,439 and 4,876 participants, respectively. After Bonferroni correction and covariate adjustments, a higher MSSS was associated with 37 coexisting conditions in the discovery cohort. Subsequently, 16 conditions, including genitourinary, infectious, metabolic, epileptic, and movement disorders, met the reporting criteria, reaching the Bonferroni threshold of significance with the same direction of effect in the discovery and extension cohort. Notably, benign neoplasm of the skin was inversely associated with the MSSS.

**Conclusion** The phenome-wide approach enabled a systematic interrogation of the comorbidity burden and highlighted clinically relevant medical conditions associated with MS severity (beyond MS-specific consequences) and defines a roadmap for comprehensive investigation of comorbidities in chronic neurologic diseases. Further prospective investigation of the bidirectional relationship between disability and comorbidities could inform the individualized patient management.

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**Objective** To determine whether the punctuated administration of low-dose rituximab, temporally linked to B-cell hyperrepopulation (defined when the return of CD19+ B cells approximates 40%–50% of baseline levels as measured before alemtuzumab treatment inception), can mitigate alemtuzumab-associated secondary autoimmunity.

**Methods** In this hypothesis-driven pilot study, 10 patients received low-dose rituximab (50–150 mg/m2), a chimeric anti-CD20 monoclonal antibody, after either their first or second cycles of alemtuzumab. These patients were then routinely assessed for the development of autoimmune disorders and safety signals related to the use of dual monoclonal antibody therapy.

**Results** Five patients received at least 1 IV infusion of low-dose rituximab, following alemtuzumab therapy, with a mean follow-up of 41 months. None of the 5 patients developed secondary autoimmune disorders. An additional 5 patients with follow-up over less than 24 months received at least 1 infusion of low-dose rituximab treatment following alemtuzumab treatment. No secondary autoimmune diseases were observed.

**Conclusions** An anti-CD20 “whack-a-mole” B-cell depletion strategy may serve to mitigate alemtuzumab-associated secondary autoimmunity in MS by reducing the imbalance in B- and T-cell regulatory networks during immune reconstitution. We believe that these observations warrant further investigation.

**Classification of Evidence** This study provides Class IV evidence that for people with MS, low-dose rituximab following alemtuzumab treatment decreases the risk of alemtuzumab-associated secondary autoimmune diseases.

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