Lymphocyte pharmacodynamics are not associated with autoimmunity or efficacy after alemtuzumab

**Objective** To examine the association between peripheral blood lymphocyte pharmacodynamics and autoimmune adverse events (AEs) or return of disease activity in alemtuzumab-treated patients with relapsing-remitting MS.

**Methods** Patients received 2 alemtuzumab courses (12 mg/d IV; 5 days at baseline, 3 days 12 months later) in the 2-year Comparison of Alemtuzumab and Rebif Efficacy in Multiple Sclerosis studies (NCT00530348 and NCT00548405) and could then receive as-needed alemtuzumab or other disease-modifying therapy in a 4-year extension (NCT00930553). Lymphocytes were phenotyped quarterly over 2 years using fluorescence-activated cell sorting. Pharmacodynamic assessments included counts of total lymphocytes, CD3+ T cells, CD4+/CD8+ T cells (total/naive/memory/regulatory [Treg]), and CD19+ B cells (total/immature/mature/memory) and ratios of CD19+ (total/immature/mature/memory) to Treg (CD4+/CD8+) counts. Assessed autoimmune AEs included immune thrombocytopenia, nephropathies, and thyroid events. Efficacy assessments included relapses, 6-month confirmed disability worsening (CDW), and MRI disease activity.

**Results** Lymphocyte repopulation patterns, including ratios between distinct lymphocyte subsets (e.g., CD19+ to Treg cell count ratios), showed no significant differences over 2 years in patients developing/not developing autoimmune AEs, relapses, CDW, or MRI activity through 6 years following alemtuzumab. Lymphocyte kinetics were also unrelated to multiple autoimmune AEs or extreme clinical phenotypes.

**Conclusions** Repopulation kinetics of the evaluated peripheral lymphocyte subsets did not predict autoimmune AE occurrence or disease activity, including return of disease activity after 2 alemtuzumab courses. Further study is needed to investigate potential antigen-level markers of treatment response.

SHP2 inhibitor protects AChRs from effects of myasthenia gravis MuSK antibody

**Objective** To determine whether an SRC homology 2 domain-containing phosphotyrosine phosphatase 2 (SHP2) inhibitor would increase muscle-specific kinase (MuSK) phosphorylation and override the inhibitory effect of MuSK-antibodies (Abs).

**Methods** The effect of the SHP2 inhibitor NSC-87877 on MuSK phosphorylation and AChR clustering was tested in C2C12 myotubes with 31 MuSK-myasthenia gravis (MG) sera and purified MuSK-MG IgG4 preparations.

**Results** In the absence of MuSK-MG Abs, NSC-87877 increased MuSK phosphorylation and the number of AChR clusters in C2C12 myotubes with 31 MuSK-maysthenia gravis (MG) sera and purified MuSK-MG IgG4 preparations.

**Conclusions** Stimulating the agrin-LRP4-MuSK-DOK7 AChR clustering pathway with NSC-87877, or other drugs, could represent a novel therapeutic approach for MuSK-MG and could potentially improve other NMJ disorders with reduced AChR numbers or disrupted NMJs.