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Abstracts

Articles appearing in the January 2020 issue

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 [T_{reg}]), and $CD19^+$ B cells (total/immature/mature/memory) and ratios of $CD19^+$ (total/immature/mature/memory) to T_{reg} ($CD4^+/CD8^+$) 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 T_{reg} 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.

NPub.org/N2/954a

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 in vitro and in DOK7-overexpressing C2C12 myotubes that form spontaneous AChR clusters. In the presence of MuSK-MG sera, the AChR clusters were reduced, as expected, but NSC-87877 was able to protect or restore the clusters. Two purified MuSK-MG IgG4 preparations inhibited both MuSK phosphorylation and AChR cluster formation, and in both, clusters were restored with NSC-87877.

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.

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