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No Correlation Between Lymphocyte Pharmacodynamics and Autoimmune Adverse Events Following Alemtuzumab Treatment in Patients With Relapsing-Remitting Multiple Sclerosis

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SHORT TITLE: Lymphocytes and Autoimmunity Post-alemtuzumab

BACKGROUND: In the phase 3 CARE-MS I/II trials (NCT00530348/NCT00548405), 2 alemtuzumab courses significantly improved clinical/MRI outcomes versus SC IFNB-1a over 2 years in RRMS patients. The most commonly occurring autoimmune adverse event (AE) with alemtuzumab includes thyroid disease, with immune thrombocytopenia (ITP) and nephropathies occurring less frequently. Alemtuzumab efficacy was maintained in a 4-year extension (NCT00930553) in absence of continuous treatment. The effects of alemtuzumab over time may be due to its selective depletion and distinct pattern of repopulation of CD52-expressing T and B lymphocytes.

OBJECTIVE: To compare lymphocyte pharmacodynamics over Years 0–2 in alemtuzumab-treated patients with or without an autoimmune AE through Years 0–6, using pooled data from the CARE-MS I/II studies.

METHODS: Autoimmune AE monitoring occurred at baseline and monthly (ITP; nephropathies) or quarterly (thyroid) in Years 0–6 and continued for 48 months after the last alemtuzumab infusion. Lymphocytes were phenotyped by flow cytometry quarterly and at Months 1 and 13 (ie, 1 month after receiving alemtuzumab Courses 1 and 2, respectively). Pharmacodynamic assessments: total counts for lymphocytes, $CD3^+/CD4^+/CD8^+$ T cells, and $CD19^+$ B cells; subset analyses for $CD4^+/CD8^+$ T cells (naive/memory/regulatory [T_{reg}]) and $CD19^+$ B cells (immature/mature/memory); $CD19^+$ (total/immature/memory) to T_{reg} ($CD4^+/CD8^+$) cell ratios. Lymphocyte pharmacodynamics over 2

years in patients with and without autoimmune AE incidence over 6 years (core/extension studies combined) were compared.

RESULTS: No difference in total lymphocyte or subset depletion or repopulation patterns was observed over 2 years in patients with or without autoimmune AEs through 6 years. No correlation was observed between autoimmune AEs and any $CD19^{+}/T_{reg}$ cell ratio.

CONCLUSION: The current analyses do not suggest that differences in lymphocyte depletion or repopulation kinetics predict the occurrence of autoimmune AEs in alemtuzumab-treated patients, although repopulation of specific B- or T-cell clones potentially expressing autoimmune antibodies remains to be determined.

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