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

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OBJECTIVE

- **To compare lymphocyte pharmacodynamic profiles over 2 years in alemtuzumab-treated RRMS patients who did or did not experience an autoimmune adverse event (AE) through 6 years**

CONCLUSIONS

- **The current analyses do not support the hypothesis that differences in depletion or repopulation kinetics of the tested lymphocyte populations in the first 2 years after initiating alemtuzumab have predictive value for the occurrence of autoimmune AEs over 6 years in RRMS patients**
- **Repopulation patterns of specific B-cell or T-cell clones potentially expressing autoimmune antibodies or receptors, and relevance of those patterns to autoimmune AE occurrence, remain to be determined**

INTRODUCTION

- Alemtuzumab is an anti-CD52 monoclonal antibody that is approved in >70 countries for patients with RRMS; it is administered as 2 initial courses (Course 1: treatment initiation, 12 mg/day IV on 5 consecutive days; Course 2: 12 months later, 12 mg/day on 3 consecutive days)
- In the phase 3 CARE-MS I (NCT00530348) and II (NCT00548405) trials, 2 courses of alemtuzumab demonstrated significantly greater improvements in clinical and MRI outcomes versus SC IFNB-1a over 2 years in patients with active RRMS[1,2]
- The most frequent AEs with alemtuzumab were infusion-associated reactions; other AEs of interest included autoimmune AEs[1,2]
- Efficacy was maintained over an additional 4-year extension study (CARE-MS extension [NCT00930553]; patients were thus followed up for 6 years overall); 63% of CARE-MS I and 50% of CARE-MS II patients did not receive additional alemtuzumab or other disease-modifying therapy (DMT) since the initial 2 courses[3-7]
- The effects of alemtuzumab over time may be due to its selective depletion and distinct pattern of repopulation of circulating CD52-expressing T and B lymphocytes[8,9]
  - Following depletion, a relative increase in regulatory T (T_{reg}) cells and a decrease in proinflammatory cytokines occurs, potentially leading to a rebalancing of the immune system[10,11]
  - The exact mechanism of action of alemtuzumab is not fully elucidated
- It has been hypothesized that differential lymphocyte depletion and repopulation patterns following alemtuzumab may create the environment for autoimmune events[12]
  - In addition, no biomarkers that would allow selection of patients at risk for the development of autoimmune events have been identified[13]
- This post hoc analysis examines whether lymphocyte depletion and repopulation patterns are associated with autoimmune AEs following alemtuzumab treatment

METHODS

Alemtuzumab Treatment and Autoimmune AE Monitoring

- In the CARE-MS studies, patients randomized to alemtuzumab received 12 mg/day IV on 5 consecutive days at baseline and on 3 consecutive days 12 months later[1,2]
- In the CARE-MS extension study, patients could receive additional alemtuzumab courses (12 mg/day on 3 consecutive days ≥12 months after the most recent course) as needed for relapse or MRI activity, or other licensed DMTs at the investigator's discretion[3-7]
- Autoimmune AEs were defined as either thyroid AEs (excluding asymptomatic abnormal laboratory values), immune thrombocytopenia (ITP; defined according to diagnostic criteria outlined by an international working group),[14] or autoimmune nephropathy documented at any time point within 6 years of follow-up
  - As part of the safety monitoring program, autoimmune AE surveillance occurred monthly (ITP; nephropathies) or quarterly (thyroid) and continued for 48 months after the last alemtuzumab infusion (the 48-month period restarted if patients received additional courses of alemtuzumab)

Assessment of Lymphocyte Pharmacodynamics

- Blood cell counts in the CARE-MS studies were obtained monthly; lymphocytes were phenotyped by flow cytometry quarterly and at Months 1 and 13 (ie, 1 month after receiving alemtuzumab Courses 1 and 2, respectively)
- Lymphocyte data from the CARE-MS studies were pooled for analysis (n=802); absolute cell counts were analyzed for total levels of lymphocytes, all $CD3^+$ T lymphocytes, $CD4^+$ T lymphocytes, $CD8^+$ T lymphocytes, and $CD19^+$ B lymphocytes
- A sub-study (n=146) analyzed the naive, memory, and T_{reg} subsets of $CD4^+$ and $CD8^+$ T lymphocytes and the immature, mature, and memory subsets of $CD19^+$ B lymphocytes
- The kinetic profiles of $CD19^+$ B cells (total/immature/memory) were also assessed relative to $CD4^+$ and $CD8^+$ T_{reg} cell counts
- Lymphocyte pharmacodynamics over 2 years were compared in patients with or without autoimmune AEs over 6 years

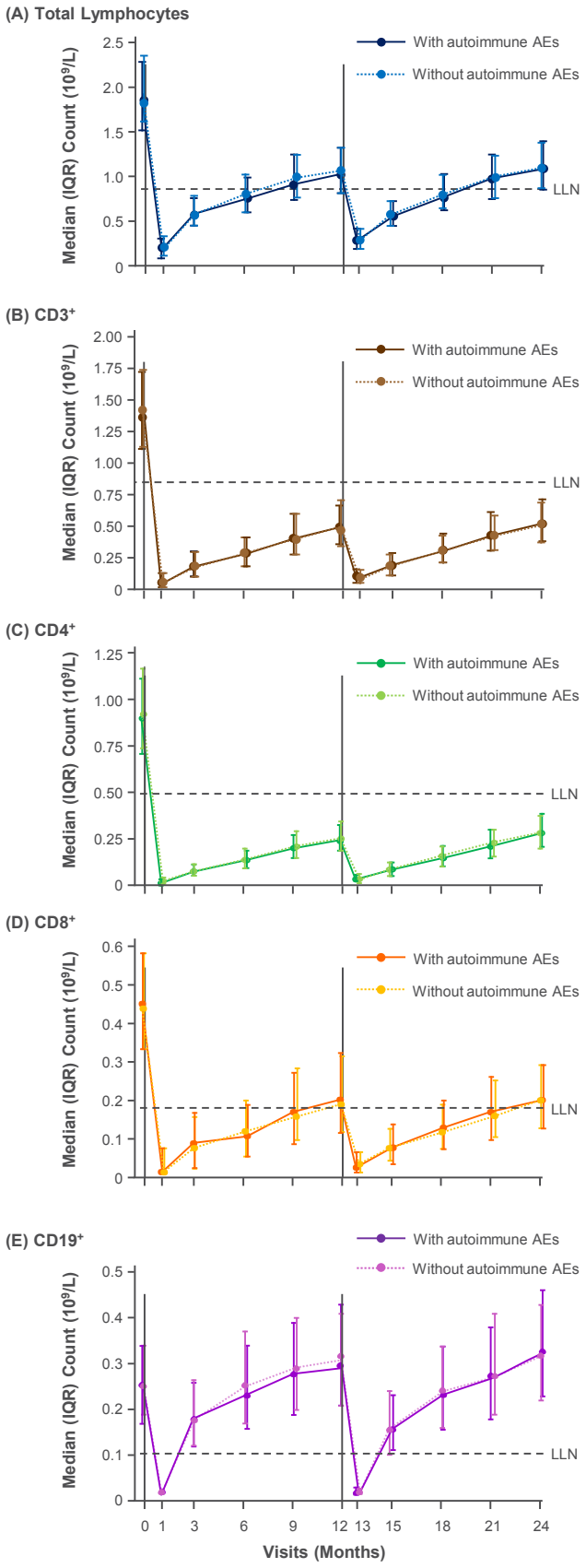
Statistical Analyses

- Linear mixed-effects models for repeated measures (MMRM) were undertaken with lymphocyte parameters as the outcome variable and autoimmune AEs, age, and baseline value as explanatory variables; models were fit for log-transformed lymphocyte data
- Multiple hypotheses testing was adjusted by using the Bonferroni correction as well as the Benjamini-Hochberg procedure[15]

RESULTS

- There was no significant overall difference in the depletion or repopulation patterns of total lymphocytes or either T or B lymphocytes over 2 years in patients who did or did not experience autoimmune AEs through 6 years following initiation of alemtuzumab treatment (**Figure 1**)

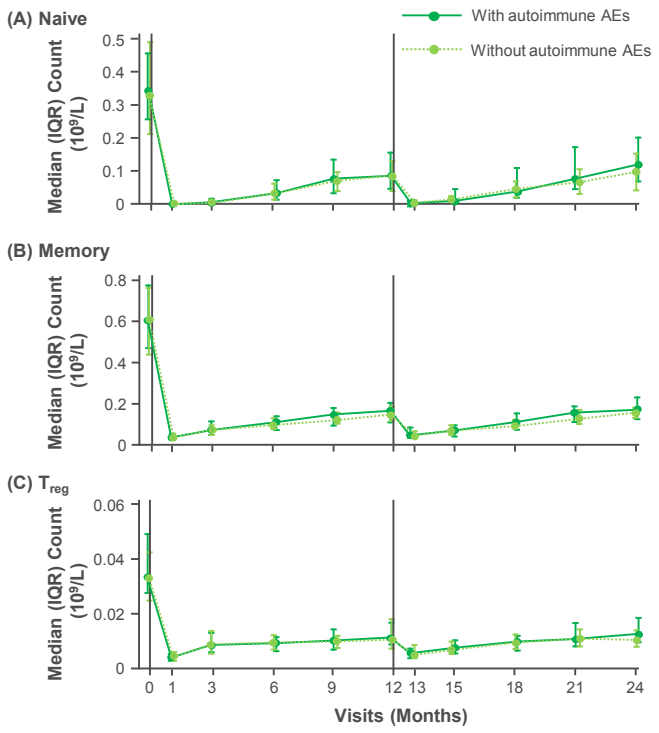
Figure 1. Median (IQR) (A) Total Lymphocyte, (B) $CD3^+$, (C) $CD4^+$, and (D) $CD8^+$ T Lymphocyte, and (E) $CD19^+$ B Lymphocyte Counts in Alemtuzumab-Treated Patients With or Without Autoimmune AEs (n=802)



IQR=interquartile range; LLN=lower limit of normal; vertical lines indicate administration of alemtuzumab

- The repopulation kinetics of $CD4^+$ lymphocyte subsets (naive, memory, and T_{reg} cells) also did not differ in patients with or without autoimmune AEs (**Figure 2**); results for $CD8^+$ and $CD19^+$ subsets were similar (data not shown)

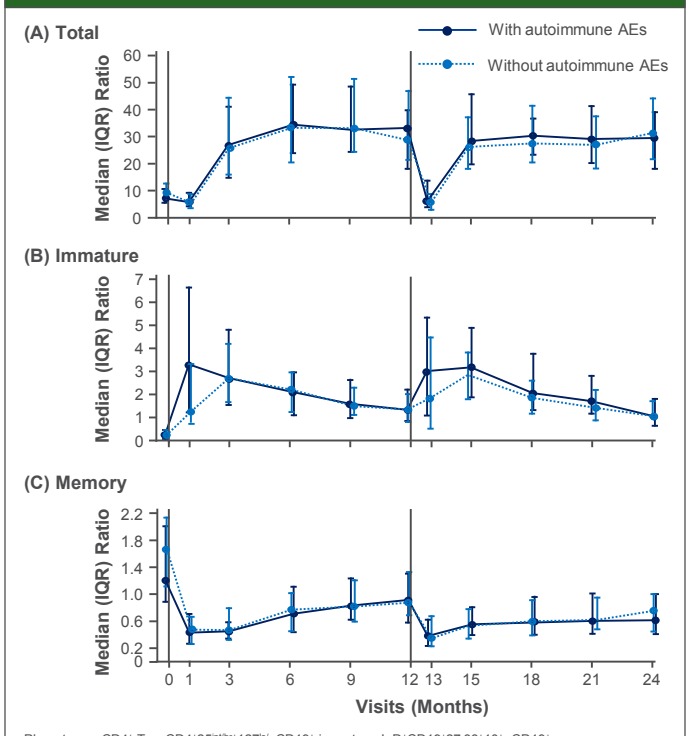
Figure 2. Median (IQR) Total $CD4^+$ (A) Naive, (B) Memory, and (C) T_{reg} Lymphocyte Counts in Alemtuzumab-Treated Patients With or Without Autoimmune AEs (n=146)



Phenotypes: $CD4^+$ naive, $CD4^+45RA^+27^+$; $CD4^+$ memory, $CD4^+45RA^-$; $CD4^+$ T_{reg}, $CD4^+25^{int/br+}127^{lo/-}$; vertical lines indicate administration of alemtuzumab

- No significant overall difference was observed between patients with or without autoimmune AEs in $CD19^+/CD4^+$ T_{reg} cell count ratios (**Figure 3**) or in $CD19^+/CD8^+$ T_{reg} ratios (data not shown)

Figure 3. Median (IQR) Ratio of Total, Immature, or Memory $CD19^+$ B Cells to $CD4^+$ T_{reg} Cells in Alemtuzumab-Treated Patients With or Without Autoimmune AEs (n=146)



Phenotypes: $CD4^+$ T_{reg}, $CD4^+25^{int/br+}127^{lo/-}$; $CD19^+$ immature, $IgD^+CD19^+27^-38^+10^+$; $CD19^+$ memory, $CD19^+27^+$; vertical lines indicate administration of alemtuzumab

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CARE-MS=Comparison of Alemtuzumab and Rebif® Efficacy in Multiple Sclerosis

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Alemtuzumab is approved in >70 countries around the world for treatment of adults with relapsing forms of multiple sclerosis (MS). In the EU, it is approved to treat patients with relapsing-remitting MS with active disease defined by clinical or imaging features. In the US, the indication provides that, because of its safety profile, the use of alemtuzumab should generally be reserved for patients who have had an inadequate response to 2 or more drugs indicated for the treatment of MS. This material may contain information that is outside of the approved labeling in some countries.

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