
- Multiple hypotheses testing was adjusted by using the Bonferroni correction.
- Linear mixed-effects models for repeated measures (MMRM) were used to analyze the data.

Statistical Analyses
- Lymphocyte data from the CARE-MS studies were pooled for analyses.
- Statistical models were adjusted to account for baseline values and treatment effects.

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 AE 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.

RESULTS
- There was no significant overall difference in the depletion or repopulation patterns of total lymphocytes or T or B lymphocytes over 2 years in patients who did or did not experience autoimmune AE over 6 years following initiation of alemtuzumab treatment (Figure 1).
- The repopulation kinetics of CD4+ lymphocyte subsets (naive, memory, and Treg cells) also did not differ in patients with or without autoimmune AE (Figure 2).

Figure 1. Median (IQR) of (A) Total Lymphocytes, (B) CD19+, (C) CD4+, and (D) CD8+ Lymphocyte Counts in Alemtuzumab-Treated Patients With or Without Autoimmune AE (n=508).

Figure 2. Median (IQR) of Total CD4+ (A) Naive, (B) Memory, and (C) Treg Lymphocyte Counts in Alemtuzumab-Treated Patients With or Without Autoimmune AE (n=486).

Figure 3. Median (IQR) Ratio of Total, Immature, or Memory CD19+ B Cells to CD4+ Treg Cells in Alemtuzumab-Treated Patients With or Without Autoimmune AE (n=146).

METHODS

Alemtuzumab Treatment and Autoimmune AE Monitoring
- In the CARE-MS studies, patients randomized to alemtuzumab received 12 mg/day IV for 5 consecutive days at baseline and then 12 mg/day every 3 months for up to 6 years.
- In the CARE-MS extension study, patients received additional alemtuzumab courses (12 mg/day for 3 consecutive days) as needed for relapse or fortractable disease.
- Autoimmune AEs were defined as either predefined AEs (including asymptomatic elevations in liver enzymes, immune thrombocytopenia, infections) or as AEs described in the labeling.

Assessment of Lymphocyte Pharmacodynamics
- Blood cell counts in the CARE-MS studies were obtained monthly; lymphocytes were phenotyped by flow cytometry quarterly and at Month 1 and 12 (6 months after receiving alemtuzumab; Courses 1 and 2, respectively).
- Lymphocyte data from the CARE-MS studies were pooled for analysis (n=252); absolute cell counts were analyzed for total lymphocytes, all CD3+ T lymphocytes, CD4+ T lymphocytes, CD8+ T lymphocytes, and CD19+ B lymphocytes.
- A sub-study (n=141) analyzed the naive, memory, and Treg subsets of CD4+ and CD8+ lymphocytes under a number of conditions that may affect the lymphocyte response following alemtuzumab treatment.
- CD4+ and CD8+ lymphocyte subsets were also measured by flow cytometry.
- Multiple hypothesis testing was adjusted by using the Bonferroni correction as well as the Benjamini-Hochberg correction.

Statistical Analyses
- Linear mixed-effects models for repeated measures (MMRM) were used to analyze the data.
- Statistical models were adjusted to account for baseline values and treatment effects.
- Multiple hypothesis testing was adjusted by using the Bonferroni correction as well as the Benjamini-Hochberg correction.

Acknowledgments and Disclosures
- The authors report financial or material support from Biogen (Mallinckrodt and Novartis) and consulting and/or grant support from Biogen (Mallinckrodt and Novartis). The authors report no other potential conflicts of interest.

REFERENCES

Figure 1 shows a comparison of lymphocyte counts between patients with and without autoimmune AEs. Figure 2 and Figure 3 illustrate the repopulation kinetics of specific lymphocyte subsets in patients with or without autoimmune AEs.