Antidrug Antibodies Have Minimal Impact on the Pharmacodynamic Profile and Clinical Efficacy of Alemtuzumab in RRMS Patients From the CARE-MS Studies

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Objective: To determine the effect of antidrug antibodies (ADAs) on the pharmacodynamics (PD)/efficacy of alemtuzumab in CARE-MS patients.

Background: In the CARE-MS studies (NCT00530348; NCT00548405), 2 courses of alemtuzumab (12 mg/day; baseline: 5 days; 12 months later: 3 days) significantly improved clinical/MRI outcomes versus SC IFNB-1a over 2 years in RRMS patients. Efficacy was maintained in 2 consecutive extensions (NCT00930553; NCT02255656 [TOPAZ; ongoing]), wherein patients could receive additional alemtuzumab courses.

Design/Methods: Alemtuzumab-binding ADA status (ever positive/always negative) was evaluated after Course (C) 2 and after additional alemtuzumab courses (C3 and C4, if received). PD/efficacy outcomes were assessed across various ADA titer thresholds.

Results: 712/811 (87.8%) patients from the pooled CARE-MS studies were ever positive for alemtuzumab-binding ADA, including 292/323 (90.4%) and 104/118 (88.1%) patients receiving C3 and C4, respectively. Median ADA titers peaked 1 month after each treatment course and decreased >60-fold 12 months later. No difference was observed in total lymphocyte or CD4⁺ T-cell depletion/repopulation patterns after C2 between ADA-positive or -negative patients; no ADA effect was observed on CD4⁺ T-cell depletion after C3. Findings in the CD4⁺ T-cell subset are representative of all major lymphocyte subsets. A year after C3, there were no significant differences between ADA-positive and -negative patients in annualized relapse rate (risk ratio [95% CI]: 0.94 [0.53–1.67]), percent relapse-free (odds ratio [95% CI]: 1.08 [0.56–2.06]), and mean change in EDSS scores (difference: 0.05; P=0.6902). Similar results were observed a year after C4. Across various titer thresholds, there was no consistent trend for an ADA effect with increasing titers.

Conclusions: Although the incidence of ADAs was high, it had minimal impact on long-term PD/efficacy after Course 2 or after additional courses (C3 and C4). These data indicate that ADAs do not limit the use of additional alemtuzumab courses to control disease activity when necessary.