INTRODUCTION

In CARE-MS I (NCT00330348) and II (NCT00544540), 2 courses of alemtuzumab provided significantly greater improvement in clinical and MRI outcomes versus SC IFNB-1a over 1 year.1,2

The most frequent adverse events (AEs) with alemtuzumab were infusion reactions, other AEs of interest included: autoimmune AEs.1,3

Alemtuzumab-treated patients who were followed for an additional 4 years in an extension study (NCT00930553) continued to show durable clinical efficacy and MRI outcomes, even though most patients (95%) did not receive additional alemtuzumab or other disease-modifying therapy (DMT).4

The estimated effects of alemtuzumab may be due to its selective depletion and distinct pattern of repopulating of circulating CD20+ lymphocytes.5

• Following depletion, a relative increase of T cells and a decrease in proinflammatory cytokines occurs, potentially leading to a reduction of the immune system’s effects.

• The exact mechanism of action is not fully elucidated.

• Delaying disease progression from RRMS to SPMS is an important endpoint of MS treatment.1,2

• Approximately half of untreated patients with RRMS will progress to SPMS within 10 years of diagnosis.4,5

• There are currently no definitive guidelines for SPMS diagnosis.6

• Lorscheider et al7 evaluated the feasibility of developing an objective definition for SPMS conversion from the MSBase registry (17,356 MS patients, median disease duration 4.8 years; median follow-up, 5.8 years).

• The original definition of SPMS consisted of disability progression by 1 EDSS point in patients with EDSS ≤5.5 or ≤6.5 EDSS points in patients with EDSS >6.5 in the absence of a relapse, a minimum EDSS score of 4 and functional system (FS) score of 2, and confirmed progression over 24 months, including progression within the FS leading to the progression event.7

• Applying this definition to the MSBase registry population resulted in a SPMS conversion rate of 18% over 5.8 years.7

METHODS

Patients

• Patients in the phase 3 CARE-MS I and II studies had active RRMS and were eligible for inclusion in the extension study if they had an inadequate response to prior therapy (CARE-MS I)2 or had relapse activity while on a DMT (CARE-MS II).3

• Treatment

• Patients in the alemtuzumab arm received 2 annual courses of alemtuzumab: 12 mg IV on 5 consecutive days at baseline and on 3 consecutive days (Courses 1 and 2).8

• In the extension study, patients could receive additional treatment with alemtuzumab (12 mg IV on 3 consecutive days d12 months after the most recent course) as needed for relapse or relapse activity, or other licensed DMTs at the investigator’s discretion.

Analysis of SPMS Conversion

• A post hoc analysis was performed to analyze the percentage of patients who converted to SPMS in the pooled CARE-MS I and II studies using the definition of SPMS conversion developed by Lorscheider et al.7

RESULTS

CONCLUSIONS

• Over 6 years of follow-up in the absence of continuous treatment, a low proportion (2.5%) of CARE-MS alemtuzumab-treated patients progressed to a SPMS definition by Lorscheider et al.12

• The results of the primary analysis were confirmed by additional sensitivity analyses.

• Possible predictive factors for SPMS progression in this analysis may include higher Gd-enhancing MRI lesion counts and greater T1 and T2 lesion volumes at baseline.

• Further confirmation of these results in real-world cohorts will be important.

SPMS Conversion

Analysing alemtuzumab-treated patients from the pooled CARE-MS I and II studies, 20 (2.5%) met the Lorscheider et al optimal definition of SPMS through 6 years.13

• All baseline, compared with patients who did not convert to SPMS, those who converted to SPMS had numerically longer RRMS disease duration, higher gadolinium (Gd)-enhancing MRI lesion counts, and greater T1 and T2 lesion volumes; higher proportions of patients also had Gd-enhancing lesions.

• In addition to the minimum score of 2 in the pyramidal FS, which was part of the definition of SPMS conversion,12 of the 20 patients who converted to SPMS had 2 other FS leading to the progression event.

• The other leading FS included: sensory (n=3), cognitive (n=3), speech (n=2), ophthalmologic (n=2), and balance (n=2).

• Of the 20 patients who converted to SPMS, 12 (60%) received no alemtuzumab retreatment in the extension (24% continued to receive only 1 retreatment (ex, alemtuzumab Course 3), and 4 (20%) received 2 retreatments (Courses 3 and 4)).

• The results of the sensitivity analyses that evaluated longer confirmation periods showed that a lower proportion of patients converted to SPMS confirmed over 6 or 12 months (Figure 2).2

• Similarly, conversion rates using a lower EDSS threshold (0.3) were also low (Figure 3).

• To estimate the number of potential SPMS converters from those for whom full 6-year data were available, 2 approaches were taken—

• First, EDSS and MRI data for those with an EDSS score of 24 and a pyramidal score of 22 at any time during their follow-up were reviewed manually.

• Of the resulting 76 patients, 4% and 2% were likely and unlikely, respectively, to have converted to SPMS, whereas the remaining 40 patients had insufficient data to determine a potential outcome.

• Among the likely converters, the pooled analysis showed that 24 patients (3.0%) met this definition of SPMS through 6 years.

• Including the likely converters, there were 25 patients (3.1%) who met this definition of SPMS through 6 years.

• Second, of the 185 patients lacking full 6-year data, those who had at least 5.7 years of data and who did not convert to SPMS during this period, as well as 4 patients who were identified as converting to SPMS before the study were excluded from the sensitivity analysis (n=46 total).

• Assuming 2.5% of the remaining 139 patients converted to SPMS (n=4), the pooled analysis showed that 24 patients (3.5%) met this SPMS definition through 6 years.

Table 1. Characteristics of Alemtuzumab-Treated Patients Who Did and Did Not Convert to SPMS (Pooled CARE-MS Studies)12

SPMS Confirmed Over 6, 12, and 24 Months. EDSS Threshold 24

Figure 3. Kaplan-Meier Estimates of SPMS Conversion Over 6 Years (Pooled CARE-MS Studies)12

Figure 1. Through 6 Years, Few Alemtuzumab-Treated Patients Converted to SPMS Confirmed Over 3 Months: Optimal Definition (EDSS Threshold 24)

Figure 2. Sensitivity Analyses Show That Few Alemtuzumab-Treated Patients Converted to SPMS Through 6 Years. Confirmed Over 3 to 24 Months. EDSS Threshold 24

References


Acknowledgments and Disclosures

CARE-MS III, Semin Neurol, and Immunology/Clinic Neuroscience have received research support from Merck Serono, Novartis, Roche, Sanofi, and Teva; member of advisory board, board of directors, or other similar group (Actelion, Bayer, Biogen, Merck Serono, Novartis, Opexa, Roche, and Sanofi); participation in speaker’s bureau (Sanofi).

Sponsorship: This study was sponsored by Sanofi and Bayer HealthCare Pharmaceuticals. The CARE-MS I, CARE-MS II, and CAMMS03409 studies were funded by Sanofi and Bayer HealthCare Pharmaceuticals.

Presented by the 25th Annual Meeting of the European Chapter of the Institute of Electrical and Electronics Engineers (EMC2016); 31st Annual Conference and Exhibition on Magnetic Resonance in Medicine (ISMRM); 31st Annual Meeting of the Canadian Academy of Radiology (CAR); 13th Annual Meeting of the American Society of Neuroradiology (ASNR); 2017 World Congress of Neurology (WCN); 58th Annual Meeting of the German Society of Neurology (DGN); 2017 Annual Meeting of the International Society for Magnetic Resonance in Medicine (ISMRM); and the 123rd Annual Meeting of the American Neurological Association (ANA). This study was self-funded, and the authors have no conflicts of interest to disclose.

Sensitivity Analyses Show That Few Alemtuzumab-Treated Patients Converted to SPMS Through 6 Years. Confirmed Over 3 to 24 Months. EDSS Threshold 24

(A) Sensitivity Analyses Show That Few Alemtuzumab-Treated Patients Converted to SPMS Through 6 Years. Confirmed Over 3 to 24 Months. EDSS Threshold 24

(B) Kaplan-Meier Estimates of SPMS Conversion Over 6 Years (Pooled CARE-MS Studies)12

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