Low Conversion Rate From Relapsing-Remitting MS to Secondary Progressive MS in Patients Treated With Alemtuzumab: 6-Year Follow-up of CARE-MS I and II

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OBJECTIVE

- **To determine the conversion rate from RRMS to SPMS through 6 years among alemtuzumab-treated patients in the CARE-MS I and II studies**

INTRODUCTION

- In CARE-MS I (NCT00530348) and II (NCT00548405), 2 courses of alemtuzumab demonstrated significantly greater improvements on clinical and MRI outcomes versus SC IFNB-1a over 2 years[1,2]
- The most frequent adverse events (AEs) with alemtuzumab were infusion-associated reactions; other AEs of interest included autoimmune AEs[1,2]
- 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 (56%) did not receive additional alemtuzumab or other disease-modifying therapy (DMT)[3-6]
- The durable effects of alemtuzumab may be due to its selective depletion and distinct pattern of repopulation of circulating CD52-expressing T and B lymphocytes[7,8]
  - Following depletion, a relative increase of T cells and a decrease in proinflammatory cytokines occurs, potentially leading to a rebalancing of the immune system[9,10]
  - The exact mechanism of action is not fully elucidated
- Delaying disease progression from RRMS to SPMS is an important treatment goal in MS
- Approximately half of untreated patients with RRMS will progress to SPMS within 10 years of diagnosis[11,12]
- There are currently no definitive guidelines for SPMS diagnosis
- Lorscheider et al[13] evaluated the feasibility of developing an objective definition for SPMS using data from the MSBase registry (17,356 MS patients; median baseline disease duration, 3.8 years; median follow-up, 5.8 years)
  - The optimal definition of SPMS consisted of disability progression by 1 EDSS point in patients with EDSS ≤5.5 or 0.5 EDSS points in patients with EDSS ≥6 in the absence of a relapse, a minimum EDSS score of 4 and pyramidal functional system (FS) score of 2, and confirmed progression over ≥3 months, including confirmation within the FS leading to the progression event[13]
  - Applying this definition to the MSBase patient population resulted in an SPMS conversion rate of 18% over 5.8 years[13]

METHODS

Patients

- Patients in the phase 3 CARE-MS I and II studies had active RRMS and were either treatment-naive (CARE-MS I) or had an inadequate response to prior therapy (CARE-MS II)[1,2]

Treatment

- Patients in the alemtuzumab arm received 2 annual courses of alemtuzumab: 12 mg/day IV on 5 consecutive days at baseline and on 3 consecutive days 12 months later
- In the extension study, patients could receive additional treatment with alemtuzumab (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

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 optimal definition of SPMS developed by Lorscheider et al[13] (following clarification from the author)
- Sensitivity analyses included:
  - Evaluation of different confirmation periods (6, 12, or 24 months)
  - Evaluation using a minimum EDSS of 3 (and 6-, 12-, or 24-month confirmation periods), which was found by Lorscheider et al to have lower specificity and lower overall accuracy than the optimal SPMS definition (particularly when using 6-month confirmation)[13]
  - Estimation of the number of patients who may have converted to SPMS but for whom full 6-year data were not available
- Analyses were performed using interim data from the extension study, and were based on all available data through Year 6 (end of extension Year 4)

RESULTS

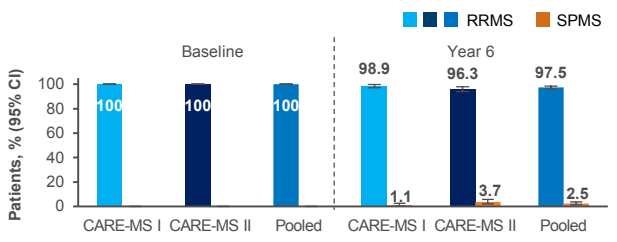
Patients

- Of the 811 alemtuzumab-treated CARE-MS I and II patients, a total of 790 (97%) completed the core studies; 742 (94%) of these patients entered the extension, of whom 669 (90%) remained on study at Year 6
- Through 6 years, 56% of pooled CARE-MS patients received no alemtuzumab retreatment or another DMT
- 59% of pooled CARE-MS patients did not receive alemtuzumab retreatment; 93% did not receive another DMT

SPMS Conversion

- Among 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] (**Figure 1**)
- At 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 volume; higher proportions of patients also had Gd-enhancing lesions (**Table 1**)
- In addition to the minimum score of 2 in the pyramidal FS, which was part of the definition of SPMS conversion,[13] 13 of the 20 patients who converted to SPMS had ≥1 other FS leading to the progression event
  - The other leading FS included cerebellar (n=8), sensory (n=3), brainstem (n=3), bladder-bowel (n=2), cerebral (n=2), and visual (n=1)
- Of the 20 patients who converted to SPMS, 12 (60%) received no alemtuzumab retreatment in the extension, 4 (20%) received only 1 retreatment (ie, 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**); no patients converted to SPMS confirmed over 24 months
  - Similarly, conversion rates using a lower EDSS threshold (≥3) were also low (**Figure 3**)

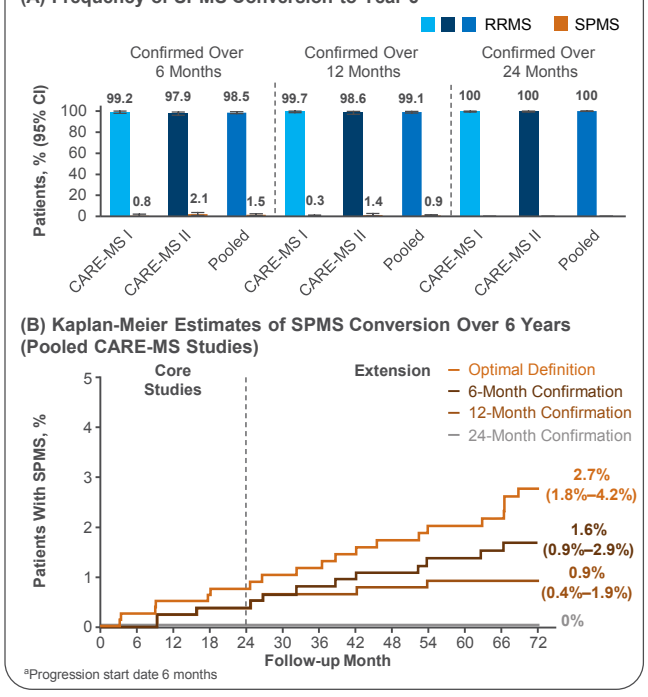
Figure 1. Through 6 Years, Few Alemtuzumab-Treated Patients Converted to SPMS[a] Confirmed Over 3 Months: Optimal Definition (EDSS Threshold ≥4)[b]



Baseline Characteristics in Patients Converting to SPMS	CARE-MS I (n=4)	CARE-MS II (n=16)	Pooled (n=20)
Duration of disease, years	2.2 (0.9)	5.2 (2.8)	4.6 (2.8)
EDSS score	2.6 (0.8)	3.6 (1.2)	3.4 (1.2)
No. of Gd-enhancing lesions	3.5 (4.0)	6.8 (7.9)	6.1 (7.3)
Proportion with Gd-enhancing lesions, %	75.0	86.7	84.2
T1 hypointense lesion volume (cm^3)	1.7 (1.0)	3.4 (5.2)	3.0 (4.7)

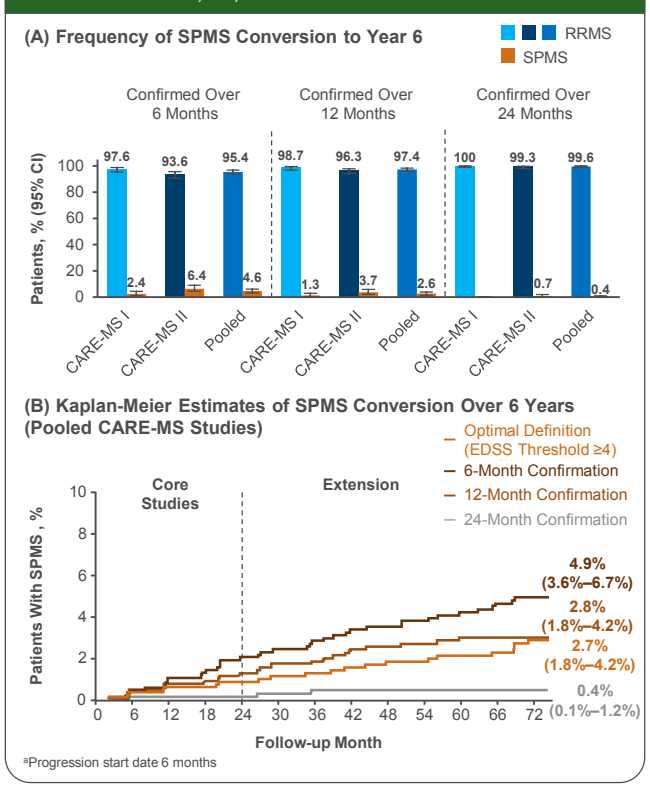
Values represent mean (SD) unless otherwise indicated. [a]Progression start date 6 months; [b]Adapted from optimal definition of SPMS as developed by Lorscheider et al[13]

Figure 2. Sensitivity Analyses Show That Few Alemtuzumab-Treated Patients Converted to SPMS[a] Through 6 Years, Confirmed Over 6, 12, and 24 Months: EDSS Threshold ≥4



[a]Progression start date 6 months

Figure 3. Sensitivity Analyses Show That Few Alemtuzumab-Treated Patients Converted to SPMS[a] Through 6 Years, Confirmed Over 6, 12, and 24 Months: EDSS Threshold ≥3



[a]Progression start date 6 months

- To estimate the number of potential SPMS converters from those for whom full 6-year data were not available, 2 approaches were taken
  - First, EDSS and relapse data for those patients with an EDSS score of ≥4 and a pyramidal score of ≥2 at any time during their follow-up were reviewed manually
    - Of the resulting 76 patients, 4 and 32 were likely and unlikely, respectively, to have converted to SPMS, whereas the remaining 40 patients had insufficient data to determine a potential outcome
    - Including the likely patients, the pooled analysis showed that 24 patients (3.0%) met this definition of SPMS through 6 years
    - Including the likely patients, and 2.5% of those for whom there were insufficient data (the percentage of converters from the main analysis), the pooled analysis showed that 25 patients (3.1%) met this definition of SPMS through 6 years
  - Second, of the 185 patients lacking full 6-year data, those who had at least 5.75 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 leaving 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 (3.0%) 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)[a]

Parameter	Pooled CARE-MS I and II	
	With SPMS (n=20)	Without SPMS (n=791)
Age at BL, years	36.6 (6.7)	33.9 (8.3)
Age at SPMS, years	40.1 (6.4)	–
EDSS score at BL	3.4 (1.2)	2.4 (1.1)
EDSS score before SPMS	3.4 (1.3)	–
EDSS score after SPMS	5.0 (1.0)	–
Years since initial relapse at BL	4.6 (2.8)	3.3 (2.4)
No. of relapses in prior 1 year at BL	1.6 (0.7)	1.7 (0.9)
No. of Gd-enhancing lesions at BL	6.1 (7.3)	2.2 (5.5)
Proportion with Gd-enhancing lesions at BL, %	84.2	43.0
T2 hyperintense lesion volume at BL (cm^3)	12.5 (10.3)	8.7 (10.9)
T1 hypointense lesion volume at BL (cm^3)	3.0 (4.7)	1.6 (3.2)
Brain parenchymal fraction at BL	0.82 (0.03)	0.82 (0.02)

Values represent mean (SD) unless otherwise indicated. [a]Adapted from optimal definition of SPMS as developed by Lorscheider et al.[13] BL=baseline

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Alemtuzumab is approved in >65 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 be reserved for patients who generally have had an inadequate response to 2 or more therapies 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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