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ALEMTUZUMAB'S EFFECTS ON DISABILITY OUTCOMES OCCUR EARLY IN CARE-MS II

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INTRODUCTION

- Alemtuzumab is a humanized monoclonal antibody that selectively targets CD52 to deplete circulating T and B lymphocytes, thought to be critical mediators of multiple sclerosis (MS) inflammatory processes[1-4]
- A distinctive pattern of T- and B-cell repopulation begins within weeks, leading to a rebalancing of the immune system[2]
- In the phase 3 Comparison of Alemtuzumab and Rebif® Efficacy in Multiple Sclerosis (CARE-MS) studies,[5,6] alemtuzumab given as 2 annual courses (at Month 0 and Month 12) showed superior efficacy over 2 years compared with subcutaneous interferon beta-1a (SC IFNB-1a, Rebif®) 44 µg given 3 times per week in patients with relapsing-remitting MS (RRMS)
  - In CARE-MS I, which enrolled treatment-naïve patients, alemtuzumab reduced the relapse rate by 55% (p<0.0001); there was a nonsignificant 30% reduction in sustained accumulation of disability (SAD) (8% of alemtuzumab-treated patients vs. 11% of SC IFNB-1a–treated patients; p=0.22)[5]
  - In CARE-MS II, which enrolled patients with disease activity despite disease-modifying therapy (DMT), alemtuzumab reduced the relapse rate by 49% (p<0.0001) and risk of SAD by 42% (p=0.0084)[6]
- The safety profile associated with alemtuzumab included infusion-associated reactions (IARs), infections of predominantly mild-to-moderate severity, and secondary autoimmunity (mainly thyroid disorders and, less frequently, immune thrombocytopenia)[5,6]

OBJECTIVE

To evaluate the timecourse of alemtuzumab's effects on secondary and tertiary disability outcomes compared with SC IFNB-1a in the CARE-MS II study (NCT00548405) of RRMS patients with disease activity on prior DMT

METHODS

Study Design

- CARE-MS II was a phase 3, global, randomized, open-label, rater- and dose-blinded, head-to-head active comparator trial of 24 months' duration
- Entry criteria included age 18–55 years, baseline Expanded Disability Status Scale (EDSS) score ≤5, MS symptom onset within 10 years, active RRMS (≥2 relapses in prior 2 years and ≥1 in the prior year), and relapse on prior DMT (≥1 relapse during treatment with IFNB or glatiramer acetate, after receiving that therapy for ≥6 months [prior treatment with other DMTs was also permitted])
- Patients were randomized to receive alemtuzumab 12 mg/day (intravenous [IV] once daily on 5 consecutive days at Month 0 and 3 consecutive days at Month 12) or IFNB-1a (44 µg SC 3 times weekly)
- Patients received methylprednisolone (1 g/day IV) for 3 days at Months 0 and 12 in both treatment arms for unbiased prophylaxis of IARs in the alemtuzumab-treated patients

Disability Outcomes

- Change from baseline on EDSS (secondary endpoint)
  - EDSS was assessed at baseline and every 3 months thereafter
  - Performed by qualified blinded raters
- Time to 6-month sustained reduction in disability (SRD; tertiary endpoint)
  - Defined as a ≥1 point decrease from baseline EDSS for patients with baseline EDSS ≥2, sustained for 6 months
- MS Functional Composite (MSFC) Z-scores change from baseline (secondary endpoint)
  - The MSFC is an objective and quantitative measure of disability comprising 3 component tests: ambulation, cognition, and arm function and was scored using the MSFC Scoring Manual guidelines, which describes standardization of the MSFC components into Z-scores
  - MSFC was assessed at baseline and every 6 months thereafter
  - Performed by qualified blinded raters
- MSFC plus Sloan chart Z-scores change from baseline (tertiary endpoint)
  - Incorporates Sloan low-contrast visual letter acuity testing as a fourth component of the MSFC to capture visual dysfunction as an additional dimension of disability
  - Sloan chart testing using 2.5% contrast level occurred at baseline and every 6 months thereafter
  - Performed by qualified blinded raters

Statistical Analysis

- Wei-Lachin test and mixed model for repeated measures analyses with a time by treatment interaction and covariate adjustment for geographic region and the corresponding baseline score, for change from baseline on EDSS, MSFC Z-scores, and MSFC plus Sloan 2.5% Z-scores[7]
- Kaplan-Meier analysis of time to 6-month SRD and hazard ratio from proportional hazards regression stratified by baseline EDSS with robust variance estimation and covariate adjustment for geographic region

RESULTS

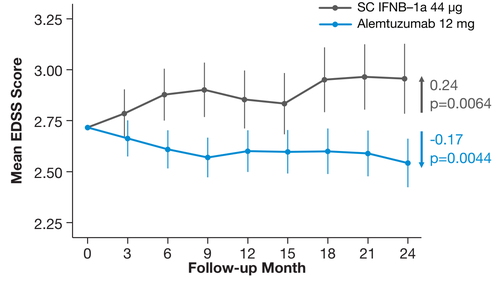
Patients

- Baseline demographic and disease characteristics were similar between treatment groups, as previously reported[6]
  - Mean age was 35 years
  - 66.7% were women
  - Mean number of years since onset of MS symptoms was 4.5
  - Baseline mean EDSS score was 2.7

EDSS and SRD over Time

- **Figure 1** illustrates the mean EDSS score over time
  - From Month 6 onwards, alemtuzumab-treated patients showed significant mean improvement from baseline (all p values <0.05), whereas SC IFNB-1a–treated patients showed significant mean worsening from baseline at most time points
  - The difference between treatment groups in mean EDSS scores was statistically significant by Month 6, with a net difference of 0.27 (p=0.0003), and was maintained throughout the 2-year study

Figure 1. Mean EDSS Score over Time

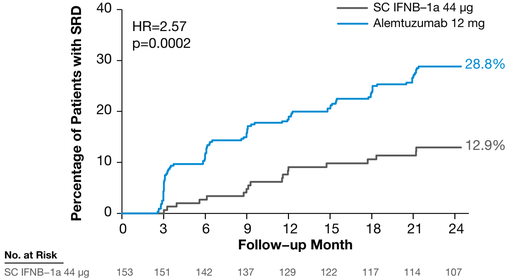


	Month	3	6	9	12	15	18	21	24
Change from Baseline	SC IFNB-1a 44 µg	NS p=0.26	Worsened p=0.0130	Worsened p=0.0069	NS p=0.06	NS p=0.13	Worsened p=0.0039	Worsened p=0.0025	Worsened p=0.0064
	Alemtuzumab 12 mg	NS p=0.23	Improved p=0.0248	Improved p=0.0031	Improved p=0.0258	Improved p=0.0290	Improved p=0.0411	Improved p=0.0261	Improved p=0.0044
	Group difference	NS p=0.07	p=0.0003	p<0.0001	p=0.0023	p=0.0073	p=0.0002	p<0.0001	p<0.0001

EDSS=Expanded Disability Status Scale; NS=not significant; SC IFNB-1a=subcutaneous interferon beta-1a

- Over 2 years, alemtuzumab-treated patients were more than twice as likely to experience a 6-month SRD compared with SC IFNB-1a–treated patients (p=0.0002), with the difference apparent as early as Month 6 (**Figure 2**)

Figure 2. Time to 6-month SRD



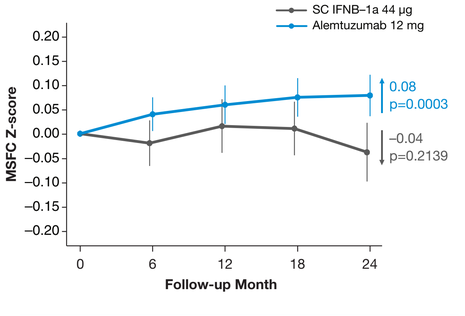
No. at Risk										
SC IFNB–1a 44 µg	153	151	142	137	129	122	117	114	107
Alemtuzumab 12 mg	321	321	290	275	262	254	245	235	213

HR=hazard ratio; SC IFNB-1a=subcutaneous interferon beta-1a; SRD=sustained reduction in disability

MSFC and MSFC Plus Sloan 2.5% over Time

- **Figure 3** illustrates the mean MSFC Z-score over time, with higher scores indicating improvement and lower scores indicating worsening of disability
  - From Month 6 onwards, alemtuzumab-treated patients showed significant mean improvement from baseline (all p values <0.05), whereas SC IFNB-1a–treated patients showed no significant mean change from baseline at Months 6, 12, 18, or 24
  - The difference between treatment groups in mean MSFC Z-scores was statistically significant by Month 6, with a net difference of 0.06 (p=0.0236)
  - The difference between groups was maintained throughout the 2-year study, with p values <0.05 except at Month 12

Figure 3. Mean MSFC Z-score over Time

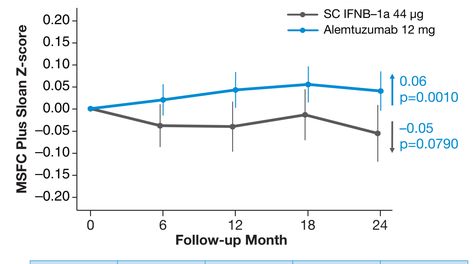


	Month	6	12	18	24
Change from Baseline	SC IFNB-1a 44 µg	NS p=0.42	NS p=0.58	NS p=0.71	NS p=0.21
	Alemtuzumab 12 mg	Improved p=0.0245	Improved p=0.0033	Improved p=0.0002	Improved p=0.0003
	Group difference	p=0.0236	NS p=0.16	p=0.0425	p=0.0009

MSFC=MS Functional Composite; NS=not significant; SC IFNB-1a=subcutaneous interferon beta-1a

- Over 2 years, alemtuzumab-treated patients also improved significantly more in MSFC plus Sloan 2.5% Z-score compared with SC IFNB-1a–treated patients (p=0.0011 at Month 24); statistical significance was achieved by 6 months and maintained throughout the study period (**Figure 4**)

Figure 4. Mean MSFC Plus Sloan 2.5% Z-score over Time



	Month	6	12	18	24
Change from Baseline	SC IFNB-1a 44 µg	NS p=0.16	NS p=0.46	NS p=0.85	NS p=0.08
	Alemtuzumab 12 mg	Improved p=0.0081	Improved p=0.0011	Improved p<0.0001	Improved p=0.0010
	Group difference	p=0.0083	p=0.0154	p=0.0328	p=0.0011

MSFC=MS Functional Composite; NS=not significant; SC IFNB-1a=subcutaneous interferon beta-1a

CONCLUSIONS

- Findings on secondary and tertiary disability endpoints in CARE-MS II support the demonstration of superiority of alemtuzumab vs. SC IFNB-1a on the primary disability endpoint of sustained accumulation of disability
- Alemtuzumab treatment led to disability reduction that developed by Month 6 and was durable through the 2-year study period
  - EDSS mean change data were supported by analyses of sustained reduction in disability, demonstrating that the reduction in EDSS scores observed are meaningful and durable
  - MSFC and MSFC plus Sloan data independently corroborate the functional improvement observed after alemtuzumab treatment
- These findings, together with previously reported data, support the positive benefit-risk profile for alemtuzumab as a potential treatment for RRMS

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