Alemtuzumab improves preexisting disability in active relapsing-remitting MS patients

ABSTRACT

Objective: To characterize effects of alemtuzumab treatment on measures of disability improvement in patients with relapsing-remitting multiple sclerosis (RRMS) with inadequate response (≥1 relapse) to prior therapy.

Methods: Comparison of Alemtuzumab and Rebif Efficacy in Multiple Sclerosis (CARE-MS) II, a 2-year randomized, rater-blinded, active-controlled, head-to-head, phase 3 trial, compared efficacy and safety of alemtuzumab 12 mg with subcutaneous interferon-β-1a (SC IFN-β-1a) 44 μg in patients with RRMS. Prespecified and post hoc disability outcomes based on Expanded Disability Status Scale (EDSS), Multiple Sclerosis Functional Composite (MSFC), and Sloan low-contrast letter acuity (SLCLA) are reported, focusing on improvement of preexisting disability in addition to slowing of disability accumulation.

Results: Alemtuzumab-treated patients were more likely than SC IFN-β-1a-treated patients to show improvement in EDSS scores (p < 0.0001) on all 7 functional systems. Significantly more alemtuzumab patients demonstrated 6-month confirmed disability improvement. The likelihood of improved vs stable/worsening MSFC scores was greater with alemtuzumab than SC IFN-β-1a (p = 0.0300); improvement in MSFC scores with alemtuzumab was primarily driven by the upper limb coordination and dexterity domain. Alemtuzumab-treated patients had more favorable changes from baseline in SLCLA (2.5% contrast) scores (p = 0.0014) and MSFC + SLCLA composite scores (p = 0.0097) than SC IFN-β-1a-treated patients.

Conclusions: In patients with RRMS and inadequate response to prior disease-modifying therapies, alemtuzumab provides greater benefits than SC IFN-β-1a across several disability outcomes, reflecting improvement of preexisting disabilities.

Classification of evidence: This study provides Class I evidence (based on rater blinding and a balance in baseline characteristics between arms) that alemtuzumab modifies disability measures favorably compared with SC IFN-β-1a. Neurology® 2016;87:1985-1992

GLOSSARY

9-HPT = 9-Hole Peg Test; ANCOVA = analysis of covariance; AUC = area under the curve; CARE-MS II = Comparison of Alemtuzumab and Rebif Efficacy in Multiple Sclerosis II; CDI = confirmed disability improvement; CDW = confirmed disability worsening; DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; GA = glatiramer acetate; HR = hazard ratio; IFN-β-1a = interferon-β-1a; MS = multiple sclerosis; MSFC = Multiple Sclerosis Functional Composite; OR = odds ratio; RRMS = relapsing-remitting multiple sclerosis; SC = subcutaneous; SLCLA = Sloan low-contrast letter acuity.

Limiting disability is a major objective in multiple sclerosis (MS) care. Most disease-modifying therapies (DMTs) approved for relapsing-remitting MS (RRMS) delay confirmed disability worsening (CDW) vs placebo, based on Expanded Disability Status Scale (EDSS) outcomes.1-7 Interest is growing in aiming for confirmed disability improvement (CDI), a higher

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standard for therapeutic efficacy than merely slowing disability accumulation. Because disability is a primary contributor to the burden of MS,8–10 restoring function in patients with previously acquired neurologic impairments may lead to improved long-term prognosis, greater productivity and quality of life, and reduced economic costs.

CDI is a metric reflecting durable and clinically meaningful EDSS score changes. In the phase 2 trial of alemtuzumab for RRMS (CAMMS223; NCT00050778) and the phase 3 Comparison of Alemtuzumab and Rebif Efficacy in Multiple Sclerosis II (CARE-MS II; NCT00548405) trial, CDI was more likely in alemtuzumab-treated patients than those receiving subcutaneous interferon-β-1a (SC IFN-β-1a).11,12 In CARE-MS II, alemtuzumab was also associated with significantly greater improvement in mean EDSS and Multiple Sclerosis Functional Composite (MSFC) scores vs SC IFN-β-1a.12

The EDSS is an important tool in assessing disability, but is heavily weighted toward ambulation and relatively insensitive to other aspects of disability.13,14 We therefore analyzed disability using EDSS-based and non-EDSS-based methods. The results of these prespecified outcomes and post hoc analyses from CARE-MS II more fully characterize the effects of alemtuzumab on disability in patients with RRMS than those published previously,12 and indicate potential for long-term improvement.

METHODS Patients and study design. Methods have been published elsewhere.12 CARE-MS II was a 2-year, randomized, rater-blinded, active comparator-controlled, head-to-head, trial of alemtuzumab (Lemtrada; Sanofi Genzyme, Cambridge, MA; 12 mg/day on 5 consecutive days at month 0 and on 3 consecutive days at month 12) vs SC IFN-β-1a (Rebif; EMD Serono, Rockland, MA; 44 µg 3 times weekly) in patients with RRMS with inadequate response to prior DMTs (≥1 relapse during IFN-β or glatiramer acetate [GA] treatment [received for ≥6 months]).12

Disability assessment procedures. Differences in study drug administration and unique adverse event profiles precluded effective double blinding. Blinded raters performed EDSS assessments at baseline, every 3 months, and when relapse was suspected. EDSS score changes of ≥1 point, confirmed over 3 or 6 months or longer, are accepted as clinically meaningful.15

Raters administered the MSFC16 3 times before baseline to attenuate practice effects, then every 6 months. MSFC is a multidimensional instrument comprising quantitative tests of neurologic performance in 3 critical domains: upper limb coordination and dexterity (9-Hole Peg Test [9-HPT], raw score measured in seconds); ambulation (25-Foot Timed Walking test, raw score measured in seconds); and cognitive function (Paced Auditory Serial Addition Test [PASAT]–3, raw score measured as number of correct responses). MSFC component scores were standardized by conversion into Z scores (SD units from mean population baseline score) and averaged to a summary MSFC score; increased MSFC scores indicate improvement.17 Changes from baseline of ≥15% or ≥20% on ≥1 MSFC component score may be considered clinically meaningful.18

Visual function was assessed every 6 months using binocular Sloan low-contrast letter acuity (SLCLA). Sloan charts display alphabetic characters with various visual contrast differentials (1.25%, 2.5%, and 100%, ranging from light gray to black); scores represent the number of correctly identified letters (maximum 70). Increased or decreased SLCLA counts of ≥5 letters at 100% contrast, or ≥7 letters at 1.25% and 2.5% contrast, were defined as clinically meaningful improvements or decrements, respectively, as per prior MS studies.19 SLCLA was not assessed at Russian and Ukrainian sites because Latin alphabetic characters in Sloan charts may be unfamiliar in these countries. SLCLA was normalized in the same manner as MSFC components. Patients were also assessed using the 4-component, MSFC plus SLCLA score incorporating Z scores from binocular, 1.25% contrast testing.20 Previous work showed that 1.25% contrast provided the greatest capacity to detect visual dysfunction in patients with MS vs healthy controls.20

Endpoints. The following CARE-MS II tertiary endpoints were assessed: time to CDI (≥1 MSFC component score sustained for ≥3 or ≥6 months, in patients with baseline score ≥2.0); proportion worsened (≥0.5-point increase), stable, or improved (≥0.5-point decrease) from baseline EDSS; mean change from baseline in MSFC and MSFC plus SLCLA scores and their components; and proportions worsened (≥0.5 SD decrease), stable, or improved (≥0.5 SD increase) from baseline MSFC scores.

Additional analyses included integrated disability score of area under the curve (AUC20,21 and AUCCHANGE as previously described21) for EDSS from quarterly visits over 2 years (considered more sensitive than CDI Kaplan-Meier analysis)21 and odds ratios (ORs) for improvement vs stability or worsening on individual EDSS functional systems (visual [optic], brainstem, pyramidal, cerebellar, sensory, bowel/bladder, and cerebral [mental]) from baseline to month 24. To determine whether disability improvement was confounded by recovery from recent relapse, we compared mean EDSS change from baseline to month 6 in patients with and without recent prestudy relapse (i.e., ≤3 months before first study treatment). To determine dependence of disability improvement on relapse suppression by alemtuzumab,22 we compared mean EDSS change from baseline to month 6 in patients with and without early on-study relapse (i.e., relapse [per protocol definition] ≤6 months after first treatment).22 Risk of disability progression based on ≥20% or ≥15% changes from baseline on ≥1 MSFC component sustained for ≥6 months was also assessed.22,23

Statistical analyses. Kaplan-Meier analyses were used to estimate risk for 3-month CDI (post hoc analysis) and 6-month CDI and risk for achieving specific (≥20% or ≥15%) MSFC improvement or worsening thresholds. Hazard ratios (HRs) and p values were generated using proportional hazards regression with covariate adjustment for geographic region and, for CDI endpoints, stratification by baseline EDSS. Integrated disability score of AUC for EDSS to 2 years (post hoc analysis) was calculated using the trapezium rule with EDSS score at all preplanned scheduled visits.21 EDSS AUC analysis used ranked
analysis of covariance (ANCOVA) models with baseline EDSS and geographic region as covariates.

Changes from baseline on MSFC component Z scores, overall MSFC score, and MSFC plus SLCLA scores were analyzed using the Wei-Lachin test and mixed model for repeated measures analyses with time-by-treatment interaction and covariate adjustment for geographic region and baseline score. The nonparametric Wei-Lachin multivariate test was used with repeated measures data using change from baseline at different timepoints to determine differences in score distribution over time between treatment groups.24 SLCLA was analyzed by ranked ANCOVA with covariate adjustment for geographic region and baseline score. Proportional odds models with covariate adjustment for geographic region and baseline EDSS or MSFC scores were used to analyze proportion worsened, stable, or improved on EDSS and MSFC. Odds of improvement vs stability or worsening on individual EDSS functional systems were determined with covariate adjustment for geographic region and baseline EDSS score.

Reported p values are nominal and not adjusted for multiple comparisons.

**RESULTS** In total, 202 and 426 CARE-MS II patients were randomized to SC IFN-β-1a 44 μg and alemtuzumab 12 mg, respectively.12 Baseline demographic and clinical characteristics were equivalent between treatment groups, as previously reported.12 Percentage of patients with recent prestudy relapse was also equivalent between groups (alemtuzumab, 32%; SC IFN-β-1a, 33%).

**EDSS-based disability outcomes.** From baseline to month 24, alemtuzumab patients were more likely than SC IFN-β-1a patients to show EDSS improvement (p < 0.0001; figure 1A). Odds of improvement in all 7 EDSS functional systems were also greater for alemtuzumab than SC IFN-β-1a (figure 1B), reaching statistical significance in 5 domains (cerebral, cerebellar, sensory, pyramidal, and visual).

Alemtuzumab patients were more than twice as likely as SC IFN-β-1a patients to experience 3-month CDI (34.7% vs 19.4%, p = 0.0003 [HR = 2.13]), consistent with previously reported 6-month CDI data (28.8% vs 12.9%, p = 0.0002 [HR = 2.57]; figure 2).12 Among patients with baseline EDSS ≥3.0, the proportion of patients with 6-month CDI was also significantly greater with alemtuzumab than SC IFN-β-1a (35.4% vs 15.3%; p = 0.0005 [HR = 2.76]). After stratification by presence or absence of prior IFN use, 6-month CDI remained consistently more likely with alemtuzumab vs SC IFN-β-1a both for patients with prior IFN use (approximately 81% of patients originally investigated in each of the 2 on-study treatment arms, 28.4% vs 12.7%, p = 0.0006 [HR = 2.64]) and patients without prior IFN use (only around 19% of patients in each group, 30.5% vs 13.9%, p = 0.0542 [HR = 3.01]).

Alemtuzumab showed beneficial effect over SC IFN-β-1a in integrated disability score AUCCHANGE [mean (SD) = 2.3 [18.45] vs 2.9 [16.84]; p = 0.0016] and AUCSUM analysis (62.8 [31.02] vs 64.8 [32.27]; p = 0.0114).

Alemtuzumab patients had comparable mean EDSS improvement from baseline to month 6 in
cohorts with or without relapse within 3 months before initiating treatment (mean change -0.1 in both relapse groups), indicating that disability improvement did not merely reflect recovery from recent relapse. SC IFN-β-1a patients experienced worsened EDSS score from baseline to month 6 (mean change +0.21 and +0.14 in cohorts with or without recent pretreatment relapse, respectively); between-group differences were significant in both cohorts (recent pretreatment relapse, \( p = 0.0203 \); no recent pretreatment relapse, \( p = 0.0065 \)).

Among patients without recent pretreatment relapse, significantly greater proportions experienced 3-month (33.8% vs 15.2%, \( p = 0.0004 \)) and 6-month CDI (28.8% vs 9.2%, \( p = 0.0002 \)) with alemtuzumab vs SC IFN-β-1a over 24 months.

In patients with early on-study relapse, mean EDSS scores increased from baseline to month 6 with both treatments (alemtuzumab, 0.44; SC IFN-β-1a, 0.37; difference 0.07; \( p = 0.7243 \)). Alemtuzumab-treated patients without early on-study relapse had improved 6-month EDSS scores; SC IFN-β-1a–treated patients showed worsening (difference -0.23; \( p = 0.0041 \)).

**MSFC-based outcomes.** The likelihood of 6-month confirmed improvement in MSFC score from baseline to month 24 was greater for alemtuzumab than SC IFN-β-1a (OR [95% confidence interval] 1.80 [1.06, 3.08]; \( p = 0.0300 \)). SC IFN-β-1a patients were significantly more likely than alemtuzumab patients to experience worsening MSFC (sustained for 6 months) at the ≥15% worsening threshold (27.58% vs 18.66%, \( p = 0.0143 \); figure 3A). At the ≥20% threshold, the proportion who experienced worsening MSFC was numerically higher with SC IFN-β-1a vs alemtuzumab, but the difference was not statistically significant (19.64% vs 13.48%, \( p = 0.0606 \)).

Among MSFC components (figure 3, B–D), the greater benefit seen at month 24 with alemtuzumab vs SC IFN-β-1a reached statistical significance for the 9-HPT (\( p = 0.0007 \)).

**SLCLA-based outcomes.** Alemtuzumab patients had more favorable visual outcomes than those receiving SC IFN-β-1a. Compared with baseline, visual acuity in alemtuzumab patients was stable at 2.5% contrast (month 12 change from baseline: 0.00; month 24: -0.01; both \( p = \text{not significant} \)) and at 100% contrast (month 12: -0.06; month 24: -0.04; both \( p = \text{not significant} \)). SC IFN-β-1a–treated patients had a significant decline in visual acuity from baseline to month 12 and from baseline to month 24 at 1.25% contrast (month 12: -0.25; month 24: -0.16; both \( p = 0.0105 \)) and 2.5% contrast (month 12: -0.20; month 24: -0.21; both \( p < 0.001 \), and 100% contrast for month 24 (-0.16; \( p = 0.0105 \)). Differences between treatment groups were significant at 2.5% contrast (month 12: \( p = 0.0005 \); month 24: \( p = 0.0014 \)) and at month 12 at 1.25% contrast (\( p = 0.0005 \)). For MSFC plus SLCLA, alemtuzumab–treated patients significantly improved from baseline to month 12 (0.04 [\( p = 0.0396 \)]); the score at month 24 increased from but did not differ from baseline (0.04 [\( p = 0.0787 \)]). SC IFN-β-1a–treated patients did not improve from baseline (month 12: -0.04 [\( p = 0.1600 \); month 24: -0.06 [\( p = 0.0876 \)]). The difference between treatment groups was significant at month 12 and month 24 (both \( p < 0.02 \); figure 3E).
DISCUSSION

Chronic disability plays a major role in the disease burden of MS. Current treatments may delay or prevent further increases in disability. However, few data exist concerning the ability of current treatments to help restore function over time in patients with previously acquired neurologic impairments, and there is a corresponding need for suitable metrics and analytic methods to reflect this novel outcome. Alemtuzumab was more effective than SC IFN-β-1a at improving disability outcomes, significantly reducing the risk of 6-month CDW, and increasing 6-month CDI. The clinical efficacy of alemtuzumab vs SC IFN-β-1a was maintained regardless of the type of prior DMTs (i.e., IFN-β-1a, IFN-β-1b, or GA). The current analysis demonstrates that, in patients with RRMS with an inadequate response to prior DMTs, alemtuzumab provides greater recovery of function across several measures.
disability measures than SC IFN-β-1a. The use of this active comparator in the CARE-MS studies set a high threshold for superiority compared with placebo-controlled studies of other DMTs.

The findings of EDSS improvement from baseline to month 24 in nearly half of the alemtuzumab-treated patients, with improvements in all 7 EDSS functional domains, suggest that such disabilities may often be reversible (at least partially) in patients with active RRMS if they receive suitable therapy, irrespective of the type of baseline functional deficit. Favorable disability outcomes were not directly attributable to relapse suppression since, in the absence of early on-study relapse, EDSS scores improved in alemtuzumab-treated patients but deteriorated in those treated with SC IFN-β-1a. Alemtuzumab also demonstrated significant improvements from baseline vs SC IFN-β-1a in mean EDSS AUC; this measure is less impacted than Kaplan-Meier analysis by transient fluctuations in EDSS scores typically observed in patients with RRMS.21 Another approach reported here is the relatively new outcome measure of CDI, which we first defined in our post hoc analysis of the phase 2 CAMMS223 trial. Rather than utilizing group means, CDI captures sustained and clinically meaningful EDSS score changes in individual patients, and thus has a simple clinical interpretation. By requiring repeated confirmation of EDSS change, it is resistant to transient fluctuations compared with single-timepoint analyses. Furthermore, this outcome only includes patients who have at least minimal preexisting neurologic impairment.15 Collectively, alemtuzumab-associated functional recovery reflected in a variety of EDSS-based measures represents an important, clinically meaningful benefit beyond slowing or preventing neurologic deterioration.

When assessing disability progression in MS, sensitivity to change can be enhanced by combining different outcome measures.14 The EDSS is the most familiar and commonly used neurologic disability index in MS trials, but has been criticized for its emphasis on ambulation and insensitivity to other disability components (e.g., cognition), especially at lower scores.15 The MSFC, which includes assessment of cognition, was selected to supplement the EDSS.14 From baseline to month 24, improvements in MSFC and MSFC plus SLCLA scores were significantly greater with alemtuzumab vs SC IFN-β-1a. Previously, MSFC worsening ($\geq 15\%$ and $\geq 20\%$ worsening from baseline on at least one MSFC component and sustained for $\geq 3$ months) was shown to correlate with EDSS, relapse rates, and some patient-reported outcomes; 15% was the more sensitive threshold to treatment effects.15 Alemtuzumab demonstrated significant benefit over SC IFN-β-1a at the 15% threshold over $\geq 6$ months. The effect of alemtuzumab differed across MSFC component scores; the strongest treatment effects were observed on the 9-HPT, indicating that improvement in upper limb function with alemtuzumab drove improvement on the MSFC composite score.

The analyses supporting DMT-induced improvement in preexisting disability reported here were prespecified and should be evaluated in the context of other published trials. The present findings are consistent with a post hoc analysis of CAMMS223,22 which enrolled treatment-naïve patients with RRMS. Improvements in preexisting disability were also reported from placebo-controlled but not active-controlled trials of natalizumab, and only using the 3-month-sustained (not 6-month) criterion,15 and from a placebo-controlled GA trial.2 In the present, active-controlled study, CDI was achieved by significantly more alemtuzumab-treated than SC IFN-β-1a-treated patients using either 3- or 6-month confirmed criteria.

The mechanisms underlying the greater observed improvement in preexisting disability after alemtuzumab are uncertain. Improvement does not reflect the expected recovery from recent prestudy relapses. Moreover, the finding that mean disability did not improve with SC IFN-β-1a even among those who had no clinically evident inflammatory activity on study suggests that disability improvement after alemtuzumab is not fully explained by superior reduction of inflammation. However, alemtuzumab’s more efficacious inhibition of CNS inflammation may provide a tissue environment that better supports endogenous remyelination and repair mechanisms. Another possible mechanism involves neurotrophic factors secreted by CNS-trafficking immune cells, which have been postulated to contribute to neuroprotection and remyelination in MS.25,26 In one study, immune cells repopulating after alemtuzumab treatment for MS secreted neurotrophic factors, including brain-derived neurotrophic factor and ciliary neurotrophic factor, after exposure to myelin basic protein in vitro.22 Further studies are necessary to confirm a role for neurotrophic mechanisms in the stabilization or improvement in disability observed in alemtuzumab-treated patients with MS.

Differences in timing, mode of administration, and side effect profiles for alemtuzumab and SC IFN-β-1a made a true double-blind design unfeasible, which may be considered a limitation of this study. However, to minimize potential bias, key efficacy assessments, including EDSS, MSFC, Sloan charts, and on-study relapses, were performed by trained evaluators blinded to treatment, and all suspected relapses were adjudicated by an independent, blinded relapse adjudication panel.

Alemtuzumab’s clinical efficacy in CARE-MS II and associated greater beneficial effects than those of
SC IFN-β-1a on disability outcomes should be considered in the context of the risks, including infusion-associated reactions, infections, and autoimmune adverse events. Measures to manage these potentially serious risks are essential for the safe use of alemtuzumab.

The outcomes presented here not only support alemtuzumab’s ability to slow disability accumulation, but also demonstrate superior benefit in improving preexisting disability in patients with RRMS with an inadequate response to prior DMT. These data add to the body of evidence supporting a favorable benefit-risk profile of alemtuzumab in the treatment of RRMS.

AUTHOR CONTRIBUTIONS
Statistical analysis was performed primarily by Stephen L. Lake (Sanofi Genzyme, Cambridge, MA). G.G., J.A.C., A.J.C., H.-P.H., E.H., K.W.S., D.H.M., M.A.P., and D.A.S.C. contributed to study design, data collection, and writing and critical review of the manuscript, and approved the final submission draft. S.L.L. led the statistical support, contributed to the writing and critical review of the manuscript, and approved the final submission draft. S.M.K. provided editorial and medical writing support (assistance in drafting the manuscript, technical editing, copyediting, and responding to reviewers’ comments).

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