Alemtuzumab versus interferon beta-1a in early relapsing-remitting multiple sclerosis: post-hoc and subset analyses of clinical efficacy outcomes

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Summary

Background **Alemtuzumab is a humanised monoclonal antibody that depletes lymphocytes, causing long-term immunomodulation. In a 3-year, rater-blinded phase 2 study (the CAMMS223 study) in patients with relapsing-remitting multiple sclerosis (RRMS), alemtuzumab reduced relapse rate and the risk of sustained accumulation of disability compared with subcutaneous interferon beta-1a, and the mean expanded disability status scale (EDSS) score of the alemtuzumab cohort improved compared with baseline. Adverse events included infusion-associated reactions, predominantly mild to moderate infections, thyroid disorders, and immune thrombocytopenia. In this study, we further analysed the CAMMS223 data with the aim of determining whether demographic and baseline disease-related characteristics affect the beneficial effects of alemtuzumab. Additionally, we aimed to describe a new outcome measure in multiple sclerosis research: sustained reduction in disability.**

Methods **334 treatment-naive patients with active, early RRMS were randomly assigned in a 1:1:1 ratio to receive interferon beta-1a (44 μg subcutaneously three times per week), or 24 mg per day or 12 mg per day alemtuzumab intravenously for 2 or 3 annual cycles. We analysed freedom from clinical disease activity (CDA; defined as no relapses and no sustained accumulation of disability) and occurrence of sustained reduction in disability (SRD; a ≥1 point decrease on the EDSS sustained for 6 consecutive months for patients with a baseline EDSS ≥2), and analysed efficacy outcomes for subgroups based on age, sex, geographic region, MRI-T1 brain volume, MRI-T2 lesion volume, disease duration, number of previous relapses within 2 years, and EDSS.**

Findings **322 patients were analysed. 161 of 215 patients treated with alemtuzumab were free of CDA at 36 months (Kaplan-Meier estimate 71·8%, 95% CI 63·1–78·8%) compared with 52 of 107 patients treated with interferon beta-1a (42·6%, 32·4–52·4%; hazard ratio [HR]=0·31, 0·20–0·46; p<0·0001). For the 199 patients with a baseline EDSS score greater than or equal to 2, SRD was more likely (HR=2·61, 1·54–4·43; p=0·0004) among patients treated with alemtuzumab (66 of 133 patients, Kaplan-Meier estimate 51·6%, 95% CI 43·2–60·7%) than patients treated with interferon beta-1a (15 of 66 patients, 27·2%, 17·2–41·4%). All disability and relapse outcomes showed evidence of beneficial effects of alemtuzumab compared with interferon beta-1a across all analysed patient subsets, and no subgroup of patients consistently responded better than others to alemtuzumab.**

Interpretation **Alemtuzumab reduced disease activity compared with interferon beta-1a in most of the analysed subgroups. Significantly greater numbers of patients experienced sustained improvement in disability after treatment with alemtuzumab than interferon beta-1a. The efficacy offered by alemtuzumab is a substantial advance in the treatment of multiple sclerosis.**

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Introduction

Alemtuzumab is a humanised monoclonal antibody that targets the cell-surface protein CD52, which is predominantly found on B and T lymphocytes;[1] the antibody rapidly depletes these lymphocytes, after which homeostatic reconstitution results in sustained alterations in T and B lymphocyte subsets.[2,3] Alemtuzumab has shown promise as a treatment for relapsing-remitting multiple sclerosis (RRMS) in early studies[4,5] and is being tested in phase 3 trials.

In open-label studies of patients with treatment-naive[4] and treatment-refractory[6] RRMS, alemtuzumab slowed—and sometimes reversed—the accumulation of disability. These studies showed that alemtuzumab would be most effective when given in the relapsing-remitting course of the disease. CAMMS223 (registered on ClinicalTrials.gov, number NCT00050778) was the first phase 2, randomised, controlled, rater-blinded clinical trial of alemtuzumab in RRMS. CAMMS223 assessed the safety and efficacy of alemtuzumab against an active comparator, subcutaneous interferon beta-1a, in drug-naive patients. Selection criteria were designed to identify patients with early, active RRMS who had not yet acquired advanced disability. Compared with interferon beta-1a, patients treated with alemtuzumab had significant reductions in relapse rate and risk of sustained accumulation of disability (SAD).[5] Furthermore,

the mean expanded disability status scale (EDSS)[7] score of the patients assigned to alemtuzumab significantly improved from baseline to month 36, but worsened in patients treated with interferon beta-1a. Notable adverse events associated with alemtuzumab included infusion-associated reactions, infections of usually mild-to-moderate severity, and autoimmunity (primarily thyroid disorders and immune thrombocytopenia).

We aimed to explore the efficacy of alemtuzumab by further analysing data from the CAMMS223 study. We report the number of patients who were free of clinical disease activity (CDA), defined as patients who experienced neither relapse nor SAD during the 36 months. Because of the improvement in mean disability after alemtuzumab reported previously,[4,5] we also describe an exploratory efficacy outcome that has recently emerged in MS research:[8] sustained reduction in disability (SRD). Finally, we test the robustness of these treatment effects in different subsets of the recruited cohort. We were especially interested in using these analyses to further define the window of opportunity for therapy in multiple sclerosis that we proposed previously;[4] therefore, we sought to determine whether age, disease duration, pre-treatment relapse history, or the presence of fixed disability or brain atrophy modify the beneficial effects of alemtuzumab.

Methods

Patients and procedures

The enrolment criteria and study design have been published previously,[5] and are briefly summarised here. From December, 2002, to July, 2004, 334 patients with untreated RRMS and EDSS scores of 3 or less, disease duration of less than or equal to 3 years, at least two relapses in the previous 2 years, and evidence of at least one gadolinium-enhancing lesion on any of up to four monthly screening MRI scans were included in the phase 2 CAMMS223 study. Ethics board approvals were obtained from all sites, and all patients provided written informed consent. Patients were randomly assigned in a 1:1:1 ratio to one of three treatment groups: subcutaneous interferon beta-1a or intravenous alemtuzumab at a dose of either 12 mg per day or 24 mg per day (one treatment cycle per year). Alemtuzumab was given for 5 days during the first treatment cycle, and for 3 days at subsequent annual cycles. The initial study lasted 36 months. Patients were not masked to treatment. In September, 2005, the data and safety monitoring board recommended suspension of alemtuzumab therapy after three patients developed immune thrombocytopenia, one of whom died. During the suspension, all safety and efficacy assessments proceeded as planned, and patients who were randomly assigned to interferon beta-1a continued to receive treatment. A programme to ensure prompt identification and management of immune thrombocytopenia was successfully implemented. The suspension was lifted in April, 2008.

The co-primary efficacy endpoints were time to SAD and relapse rate. SAD was defined as a one-point increase in EDSS score if baseline EDSS was greater than 0 (or a 1·5 point increase if baseline EDSS was 0) sustained for a continuous 6-month period. SAD sustained over 3 months is also reported to enable results to be compared with those of other trials. EDSS score was assessed at baseline and every 3 months thereafter by a neurologist masked to treatment group assignment. Precautions were taken to reduce unmasking, as described previously. Relapse was defined as new or worsening symptoms that were attributable to multiple sclerosis and associated with an objective change in neurological examination, and that lasted for at least 48 h, were present at normal body temperature, and were preceded by at least 30 days of clinical stability. Mean change in EDSS from baseline was also reported.

Post-hoc outcomes reported here are the proportion of patients free of CDA and the proportion experiencing SRD. Freedom from CDA was defined as patients who experienced neither SAD nor relapse at any time during the study; this measure is correlated with SAD-free and relapse-free status. To enable results to be compared with other trials, we include analyses for freedom from CDA at 24 and 36 months, and for CDA that includes SAD sustained over 3 or 6 months.

In developing a measure of disability improvement, we noted that a one-point change in EDSS score is widely regarded as clinically significant in the context of a sustained increase in disability. Therefore, to similarly assess a clinically significant and sustained improvement in disability, SRD was defined as a decrease in EDSS score by one point or more, sustained for a consecutive 6-month period, for patients with a baseline EDSS score of at least 2. Because 0 is the lowest value on the EDSS scale, patients with a baseline EDSS score of 0 are not assessable for SRD; therefore, in accordance with a previous study,[8] we opted to include only patients with an EDSS score of 2 or above.

Statistical analysis

Treated patients were included in the efficacy analysis. Overall treatment effects were compared for time to SAD, time to CDA, and SRD using a Cox proportional hazards model. Covariates for time to SAD and time to CDA were treatment group, baseline EDSS score, and country. For SRD analyses, treatment group was the only covariate, and only patients with baseline EDSS scores of greater than or equal to 2 were included. The estimated percentages of patients meeting SAD criteria, remaining free of CDA, and meeting SRD criteria at specific time points were generated by use of the Kaplan-Meier method. Comparisons of EDSS scores were based on repeated measures analysis of covariance with baseline EDSS, country, treatment group, visit, and treatment group by visit interaction as covariates. The annualised relapse rate was estimated using Poisson regression with

treatment group as the covariate, and inference was based on the rate ratio derived from an Andersen-Gill model with robust variance estimation and treatment group, baseline EDSS, and country as covariates.

Analyses were done within each subset of patients for each efficacy outcome. Treatment group was the only covariate in these analyses. In total, nine subsets were analysed based on prespecified baseline covariate parameters: sex, race, age, geographic region, MRI-T1 brain volume, MRI-T2 lesion volume, disease duration, number of previous relapses within 2 years, and EDSS score. An additional post-hoc subgroup analysis was done for patients treated with alemtuzumab who received only two cycles and those who received three cycles of treatment. For ordinal and nominal baseline covariates, the subsets were based on obvious or clinically meaningful groups. Subgroups for continuous baseline covariate parameters (age, MRI-T1 brain volume, MRI-T2 lesion volume, and disease duration) were defined by the observed median in the treated-patient sample. The number of patients of non-white ethnic origin was too small for reliable estimation for all endpoints analysed. Supplementary analyses were done to test for treatment-effect homogeneity by incorporating a treatment group by subgroup interaction term in each of the previously described models, with the exception of the number of alemtuzumab cycles subgroups, because the interaction term does not apply in this model. The results for each subgroup analysed in the present discussion focus on the estimation of treatment effects and not on formal statistical hypothesis testing, although an appropriate significance threshold would be 0·05/20=0·0025 to account for the 20 subgroup analyses performed for each endpoint. A nominal threshold of 0·05 was used to assess

	Interferon beta-1a (n=107)	Alemtuzumab 12 mg/day (n=107)	Alemtuzumab 24 mg/day (n=108)	Alemtuzumab pooled (n=215)	Overall (n=322)
Female	70 (65%)	69 (64%)	69 (64%)	138 (64%)	208 (65%)
White	96 (90%)	97 (91%)	96 (89%)	193 (89%)	289 (90%)
Age (years)					
Mean (SD)	32·9 (8·94)	32·2 (8·01)	32·3 (8·81)	32·3 (8·40)	32·5 (8·58)
Median (range)	31·0 (18·0–60·0)	31·0 (19·0–49·0)	31·0 (18·0–54·0)	31·0 (18·0–54·0)	31·0 (18·0–60·0)
Geographic region					
USA	56 (52%)	49 (46%)	50 (46%)	99 (46%)	155 (48%)
Europe	51 (48%)	58 (54%)	58 (54%)	116 (54%)	167 (52%)
Time since first relapse (years)					
Median (range)	1·4 (0·2–6·3)	1·3 (0·1–3·5)	1·2 (0·3–3·2)	1·2 (0·1–3·5)	1·3 (0·1–6·3)
Relapse in previous 2 years					
1	8 (7%)	5 (5%)	12 (11%)	17 (8%)	25 (8%)
2	72 (67%)	57 (53%)	56 (52%)	113 (53%)	185 (57%)
≥3	27 (25%)	43 (40%)	40 (37%)	83 (39%)	110 (34%)
MRI-T1 brain volume (mL)					
Mean (SD)	317·4 (24·82)	320·5 (27·66)	320·7 (25·06)	320·6 (26·31)	319·6 (25·83)
Median (range)	316·3 (247·7–384·8)	317·9 (265·7–385·9)	317·9 (249·2–375·0)	317·9 (249·2–385·9)	317·4 (247·7–385·9)
MRI-T2 lesion volume (mL)					
Mean (SD)	15·89 (15·27)	17·47 (24·36)	17·45 (16·78)	17·46 (20·79)	16·95 (19·14)
Median (range)	10·31 (0·07–82·56)	8·33 (0·20–192·27)	11·65 (0·30–93·82)	9·85 (0·20–192·27)	9·96 (0·07–192·27)
EDSS					
Mean (SD)	1·9 (0·84)	1·9 (0·75)	2·0 (0·74)	2·0 (0·74)	1·9 (0·78)
Median (range)	2·0 (0·0–3·5)	2·0 (0·0–3·0)	2·0 (0·0–3·5)	2·0 (0·0–3·5)	2·0 (0·0–3·5)
0	8 (7%)	4 (4%)	5 (5%)	9 (4%)	17 (5%)
1–1·5	33 (31%)	37 (35%)	36 (33%)	73 (34%)	106 (33%)
2	28 (26%)	30 (28%)	29 (27%)	59 (27%)	87 (27%)
>2	38 (35%)	36 (34%)	38 (35%)	74 (34%)	112 (35%)
Number of alemtuzumab cycles					
1	..	6 (6%)	3 (3%)	9 (4%)	..
2	..	78 (73%)	83 (77%)	161 (75%)	..
3	..	23 (21%)	22 (20%)	45 (21%)	..

Data are n (%) unless stated otherwise. EDSS=expanded disability status scale.

Table 1: **Baseline demographics and disease history**

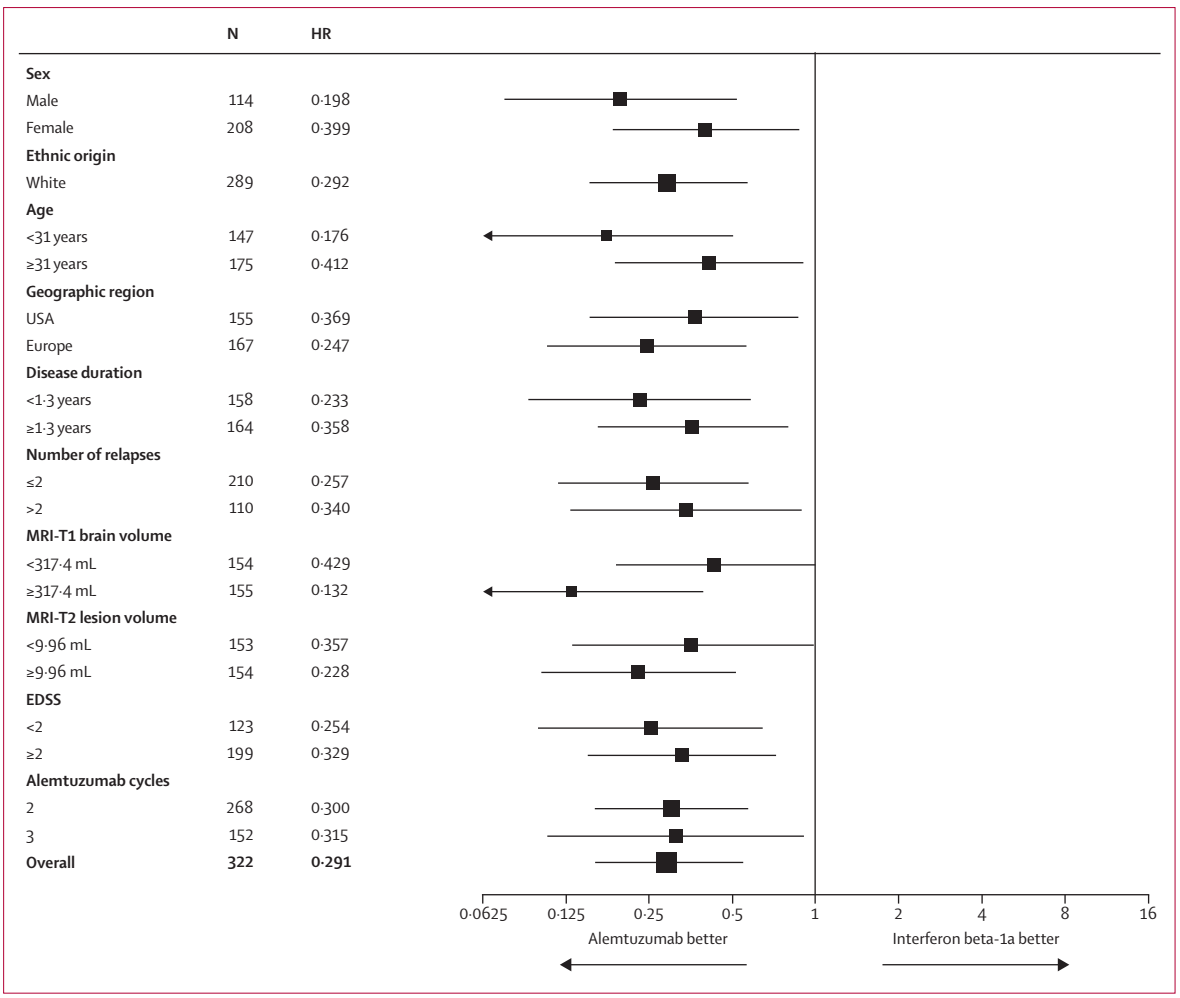

Figure 1: **Hazard ratios (HR) and 95% CIs for sustained accumulation of disability**
Box sizes are proportional to the sample size. Lines extended on either side of boxes represent the 95% confidence intervals. Specific numerical 95% CI are in webappendix pp 3–5. EDSS=expanded disability status scale. Two patients had missing data for number of relapses, 13 patients had missing data for MRI-T1 brain volume, and 15 patients had missing data for MRI-T2 lesion volume.

the significance of the treatment group by subgroup interaction models. All reported p values are two sided.

Role of the funding source

Genzyme and Bayer Schering Pharma provided financial support for the study. Genzyme participated in the design of the study, data analysis and interpretation, and preparation of this report, and MSS was subcontracted by Genzyme to assist AJC in writing the first draft of the paper. The corresponding author had full access to all the data. The decision to submit for publication was the responsibility of the corresponding author and Genzyme.

Results

Study disposition has been reported previously.[5] Briefly, 334 patients were randomly assigned to alemtuzumab or interferon beta-1a. One patient who received alemtuzumab was excluded from the efficacy analyses owing to an incorrect diagnosis of multiple sclerosis. Of the 333 patients included in the original efficacy analyses, 322 patients received treatment. Of the 111 patients assigned to receive subcutaneous interferon beta-1a three times weekly, 107 received the drug. 112 patients were assigned to 12 mg per day alemtuzumab, with 107 receiving at least one dose, and 110 patients were assigned to 24 mg per day alemtuzumab, with 108 receiving at least one dose. By the time of the suspension of alemtuzumab dosing, nine patients in the alemtuzumab groups had received only one annual cycle, 161 had received two annual cycles, and 45 had received three annual cycles. 66 of the patients treated with interferon beta-1a and 183 of the patients treated with alemtuzumab (91 in the 12 mg/day group and 92 in the 24 mg/day group) completed the 36 months of the study. More patients treated with interferon beta-1a failed to complete the study (41, 38%) than did patients treated

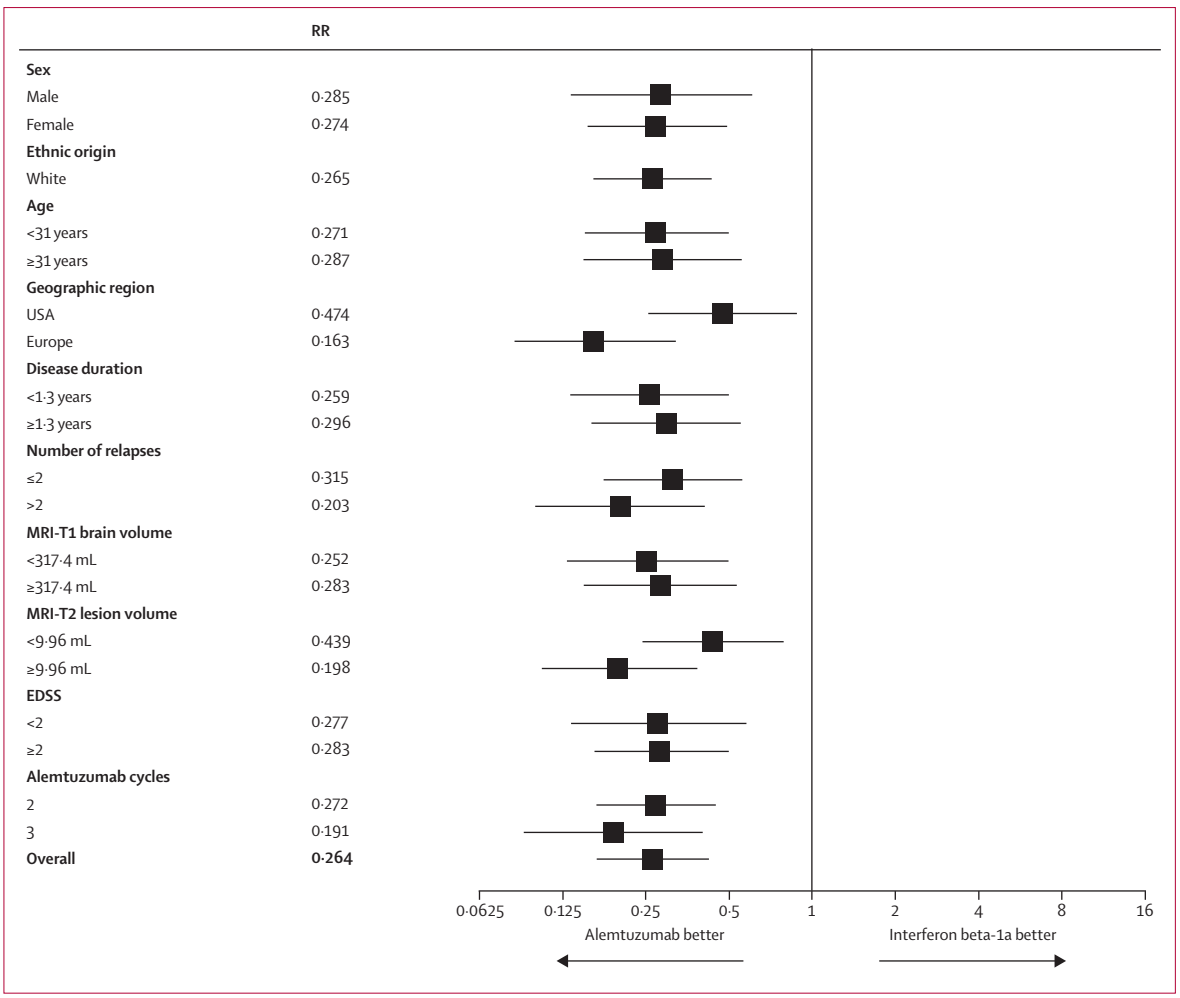

Figure 2: **Rate ratios (RR) and 95% CIs for relapse rate**
Lines extended on either side of boxes represent the 95% CIs. Specific numerical 95% CIs are in webappendix pp 6–8. EDSS=expanded disability status scale.

with alemtuzumab (32, 15%), primarily because of adverse events or lack of efficacy. Baseline demographic, geographic, and clinical disease characteristics were similar in the three treatment groups (table 1). For patients with baseline EDSS scores of 2 or higher, who could be included in the analyses for SRD, 66 patients received interferon beta-1a, 66 patients received at least one cycle of 12 mg/day alemtuzumab, and 67 patients received at least one cycle of 24 mg/day alemtuzumab. Of the 133 alemtuzumab-treated patients included in the SRD analyses, 127 received at least two cycles, and 26 received three cycles.

There were no significant differences between the two alemtuzumab dose groups for any of the clinical endpoints for the overall sample (webappendix p 1), so we report results with pooled dose groups. A breakdown according to dose is provided in the webappendix tables for the subset analyses.

See Online for webappendix

The complete analysis set for SAD is provided on webappendix pp 3–5. For treated patients, alemtuzumab reduced the risk of SAD by 70·9% (95% CI 46·1–84·3%, p=0·0001; figure 1) compared with interferon beta-1a. 197 patients treated with alemtuzumab did not experience SAD (Kaplan-Meier estimate of no event 91·2%), compared with 83 (73·8%) patients treated with interferon beta-1a. Evidence of reduced risk of SAD was found across all demographic, geographic, baseline disease characteristic of the pooled alemtuzumab groups compared with the interferon beta-1a group. The treatment effects ranged from a 57·1% (2·2–81·2%) reduction in risk of SAD for patients with an MRI-T1 brain volume less than 317·4 mL (90 [87%] patients treated with alemtuzumab with no event *vs* 41 [72%] patients treated with interferon beta-1a with no event) to an 86·8% (60·3–95·6%) reduction in risk of SAD for patients with an MRI-T1 brain volume greater than or equal to 317·4 mL (101 [96%] patients treated with alemtuzumab with no event *vs* 38 [75%] patients treated with interferon beta-1a with no event). Patients who received two cycles of alemtuzumab (n=161) experienced

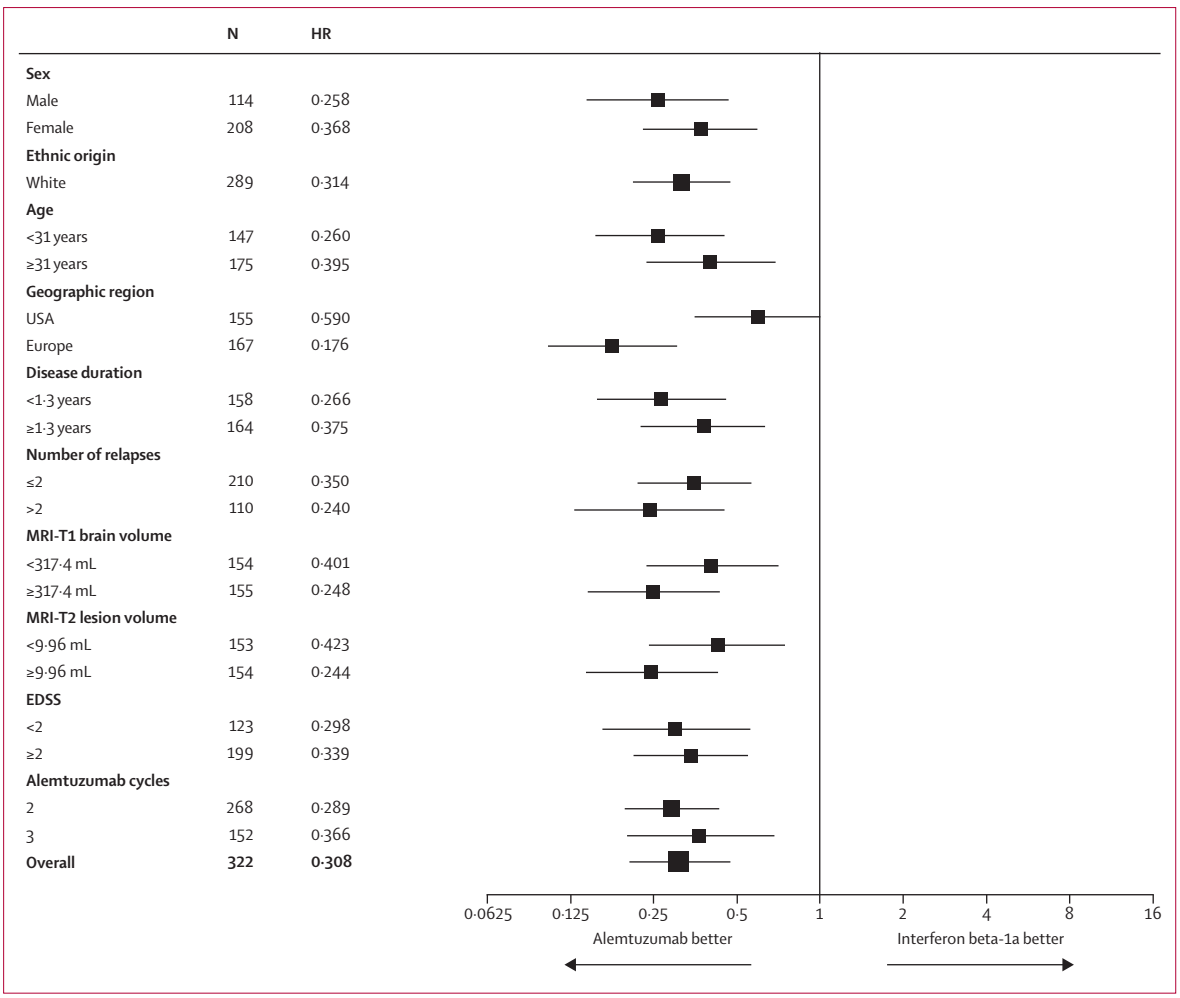

Figure 3: **Hazard ratios (HR) and 95% CIs for clinical disease activity (CDA) by subset**
Box sizes are proportional to the sample size. Lines extended on either side of boxes represent the 95% CIs. Specific numerical 95% CIs are in webappendix pp 9–11. EDSS=expanded disability status scale. Two patients had missing data for number of relapses. 13 patients had missing data for MRI-T1 brain volume, and 15 patients had missing data for MRI-T2 lesion volume.

a significant 70·0% (42·6–84·4%) reduction in risk of SAD (147 [91%] of whom had no event) compared with patients who received interferon beta-1a (83 [74%] of whom had no event), similar to the 68·5% (8·6–89·2%) reduction in risk for those patients who received three cycles of treatment (n=45; 41 [91%] of whom had no event).

The pooled alemtuzumab groups had a 73·6% (95% CI 57·9–83·5%; p<0·0001; figure 2) reduced rate of relapse (annualised relapse rate [ARR]=0·10; 0·08–0·13) compared with patients treated with interferon beta-1a (0·35; 0·29–0·43; webappendix pp 5–8). Evidence of a lower relapse rate was found across all demographic, geographic, baseline disease characteristics, and number of treatment cycle subsets of the pooled alemtuzumab groups compared with the interferon beta-1a group (figure 2 and webappendix pp 5–8), with treatment effects ranging from 52·6% (11·0–74·8%) for patients in the USA (alemtuzumab ARR 0·14, interferon beta-1a ARR 0·29) to 83·7% (68·1–91·6%) for patients in Europe (alemtuzumab ARR 0·07, interferon beta-1a ARR 0·41).

Patients treated with alemtuzumab were significantly more likely to be free of CDA (figure 3 and table 2) than were patients treated with interferon beta-1a. The estimated proportion of patients treated with alemtuzumab who were free of CDA defined by 6-month SAD at 36 months was 72% (161 patients with no event) compared with 43% (52 patients with no event) for the patients treated with interferon beta-1a (HR 0·31, 95% CI 0·20–0·46; p<0·0001). Evidence that patients in the pooled alemtuzumab group were more likely to be free of CDA than patients treated with interferon beta-1a was found across all demographic, geographic, baseline disease characteristics, and number of treatment cycles subsets (figure 3 and webappendix pp 9–11), with treatment effects ranging from 41·0% (0·8–65·5%) for

	Interferon beta-1a (n=107)	Alemtuzumab 12 mg/day (n=107)	Alemtuzumab 24 mg/day (n=108)	Alemtuzumab pooled (n=215)
2 year duration of treatment				
Freedom from relapse				
Patients free of event (n)	67	89	99	188
KM estimate of no event (95% CI)	58·5% (47·7–67·7)	82·9% (74·3–88·9)	91·6% (84·4–95·5)	87·2% (82·0–91·1)
HR (95% CI); p	..	0·324 (0·180–0·584); 0·0002	0·144 (0·067–0·311); <0·0001	0·229 (0·134–0·390); <0·0001
Freedom from 3-month SAD				
Patients free of event (n)	83	96	98	194
KM estimate of no event (95% CI)	75·3% (65·4–82·8)	89·4% (81·7–94·0)	90·6% (83·2–94·8)	90·0% (85·1–93·4)
HR (95% CI); p	..	0·379 (0·186–0·770); 0·0073	0·322 (0·153–0·676); 0·0028	0·349 (0·196–0·624); 0·0004
Freedom from 6-month SAD				
Patients free of event (n)	90	103	100	203
KM estimate of no event (95% CI)	82·5% (73·3–88·8)	96·2% (90·1–98·5)	92·4% (85·4–96·1)	94·3% (90·1–96·7)
HR (95% CI); p	..	0·195 (0·063–0·598); 0·0042	0·385 (0·167–0·885); 0·024	0·291 (0·138–0·612); 0·0011
Freedom from CDA (3-month SAD)				
Patients free of event (n)	56	82	91	173
KM estimate of no event (95% CI)	48·0% (37·6–57·6)	76·3% (67·0–83·3)	84·1% (75·6–89·8)	80·2% (74·1–84·9)
HR (95% CI); p	..	0·333 (0·204–0·544); <0·0001	0·203 (0·112–0·367); <0·0001	0·264 (0·170–0·411); <0·0001
Freedom from CDA (6-month SAD)				
Patients free of event (n)	58	87	93	180
KM estimate of no event (95% CI)	49·7% (39·2–59·3)	81·1% (72·2–87·3)	85·9% (77·7–91·3)	83·5% (77·7–87·8)
HR (95% CI); p	..	0·276 (0·159–0·479); <0·0001	0·193 (0·103–0·358); <0·0001	0·233 (0·145–0·374); <0·0001
3 year duration of treatment				
Freedom from relapse				
Patients free of event (n)	62	83	90	173
KM estimate of no event (95% CI); p	51·2% (40·1–61·3)	76·9% (67·5–83·9)	78·7% (64·3–87·8)	77·6% (69·1–84·0)
HR (95% CI)	..	0·373 (0·220–0·632); 0·0002	0·247 (0·140–0·439); <0·0001	0·307 (0·194–0·484); <0·0001
Freedom from 3-month SAD				
Patients free of event (n)	77	91	96	187
KM estimate of no event (95% CI)	66·3% (54·5–75·7)	84·2% (75·5–90·0)	88·6% (80·8–93·4)	86·4% (81·0–90·4)
HR (95% CI); p	..	0·421 (0·229–0·773); 0·0053	0·301 (0·153–0·591); 0·0005	0·359 (0·215–0·601); 0·0001
Freedom from 6-month SAD				
Patients free of event (n)	83	99	98	197
KM estimate of no event (95% CI)	73·8% (63·4–81·7)	92·0% (84·7–95·9)	90·5% (83·0–94·8)	91·2% (86·5–94·4)
HR (95% CI); p	..	0·255 (0·113–0·577); 0·0010	0·328 (0·157–0·685); 0·0030	0·291 (0·157–0·539); 0·0001
Freedom from CDA (3-month SAD)				
Patients free of event (n)	49	73	80	153
KM estimate of no event (95% CI)	38·6% (28·1–48·9)	67·3% (57·3–75·4)	68·9% (54·3–79·6)	67·7% (58·5–75·2)
HR (95% CI); p	..	0·387 (0·249–0·603); <0·0001	0·284 (0·175–0·461); <0·0001	0·333 (0·226–0·492); <0·0001
Freedom from CDA (6-month SAD)				
Patients free of event (n)	52	79	82	161
KM estimate of no event (95% CI)	42·6% (32·4–52·4)	73·1% (63·4–80·6)	71·0% (56·7– 81·3)	71·8% (63·1–78·8)
HR (95% CI); p	..	0·330 (0·203–0·537); <0·0001	0·287 (0·175–0·471); <0·0001	0·308 (0·204–0·464); <0·0001

Hazard ratios and p values are for pairwise comparisons between alemtuzumab and subcutaneous interferon beta-1a. HR=Hazard ratio. KM=Kaplan-Meier.

Table 2: **Overall treatment effect for clinical disease activity (CDA)**

patients in the USA (HR=0·59, 95% CI 0·35–1·01, for alemtuzumab compared with interferon beta-1a) to 82·4% (69·7–89·8%) for patients in Europe (HR=0·18, 0·10–0·30). At 24 months, using the 3-month SAD criteria, an estimated 80% of patients treated with alemtuzumab were free of CDA (173 patients with no event) compared with 48% of patients treated with interferon beta-1a (56 patients with no event; HR 0·26, 0·17–0·41; p<0·0001).

Annual treatment with alemtuzumab significantly increased the likelihood of achieving SRD by 36 months compared with interferon beta-1a (figure 4 and table 3). This analysis included only the 199 patients from the total cohort with a baseline EDSS score greater than or

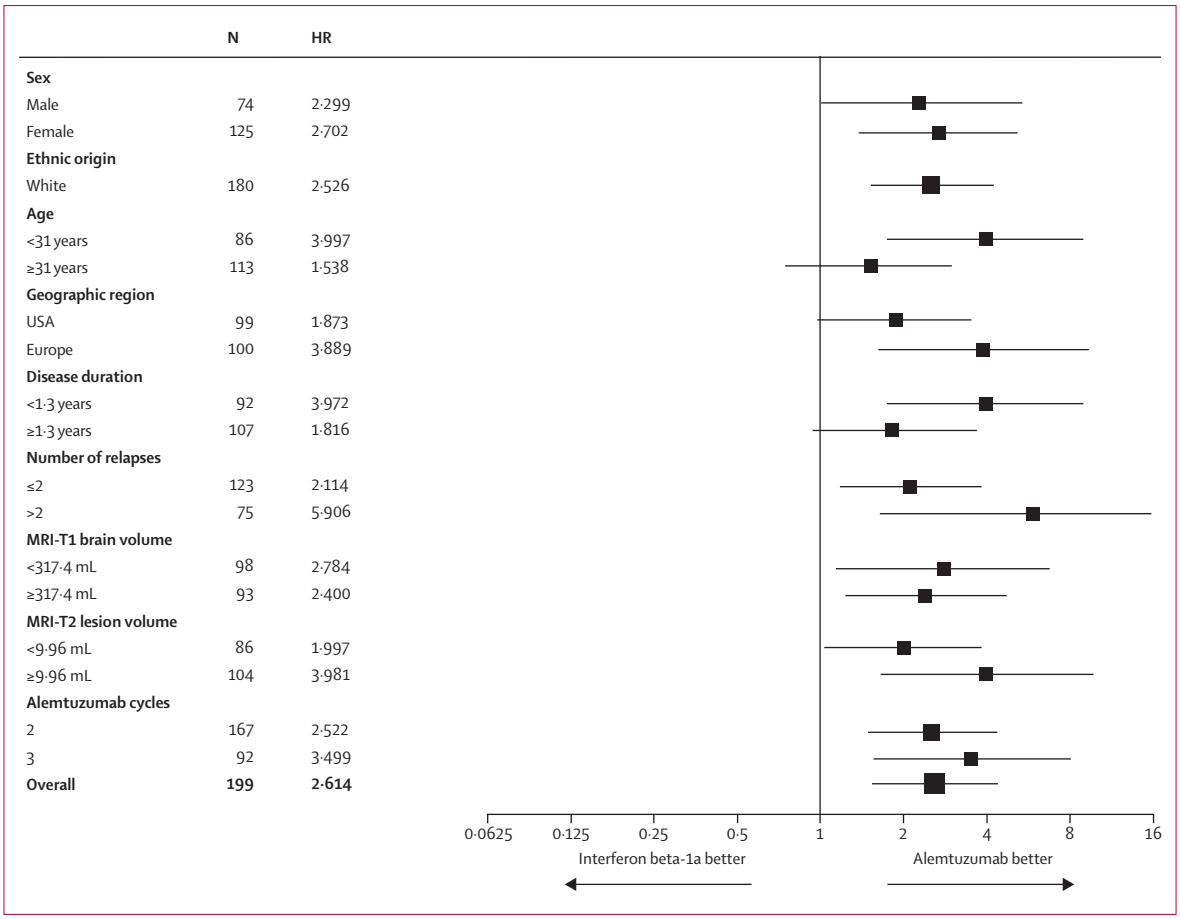

Figure 4: **Hazard ratios (HR) and 95% CIs for sustained reduction in disability**
Box sizes are proportional to the sample size. Lines extended on either side of boxes represent the 95% CIs. Specific numerical 95% CIs are in webappendix pp 12–14. One patient had missing data for number of relapses. Eight patients had missing data for MRI-T1 brain volume, and nine patients had missing data for MRI-T2 lesion volume.

equal to 2. Kaplan-Meier estimation of time to SRD by treatment group indicated that an estimated 52% of alemtuzumab-treated patients achieved SRD (66 patients with an event) compared with 27% of patients treated with interferon beta-1a (15 patients with an event; HR 2·61, 95% CI 1·54–4·43; p=0·0004). Most SRD events (67%, n=44) began in the first year after the first cycle of alemtuzumab. An additional 24% (n=16) occurred in the second year, and the remainder (9%, n=6) occurred in the third year. 12 patients treated with alemtuzumab had their EDSS score reduced to 0: five in the 12 mg/day group and seven in the 24 mg/day group. Two patients in the interferon beta-1a group improved to an EDSS score of 0. For purposes of comparison with other therapies, 2-year data on SRD were also analysed (table 3). By 2 years, an estimated 46·3% (95% CI 38·1–55·3%, n=60) of patients treated with alemtuzumab had SRD, compared with 18·5% (10·7–31·1%, n=11) of patients treated with interferon beta-1a.

Evidence that alemtuzumab increased the likelihood of achieving SRD compared with interferon beta-1a was found for most subsets of the pooled group based on demographic, geographic, baseline disease characteristics, and number of treatment cycles (figure 4 and webappendix pp 12–14). The largest treatment effect was seen in the subgroup of patients with more than two pre-treatment relapses; patients in the pooled alemtuzumab group were 5·91 (95% CI 1·61–21·67) times more likely to achieve SRD (28 [52%] patients with event) than were patients who received interferon beta-1a (two [13%] patients with event). The smallest treatment effect was noted in the subgroup of patients who were 31 years of age or older at baseline: 29 (40%) who received alemtuzumab and 9 (32%) who received interferon beta-1a achieved SRD (HR 1·54, 95% CI 0·76–3·13).

Overall, patients treated with alemtuzumab improved from baseline to month 36 after treatment by a mean of 0·39 EDSS points (95% CI 0·55–0·23; p<0·0001), whereas patients treated with interferon beta-1a underwent an increase in disability from baseline to month 36 by a mean of 0·38 EDSS points (0·13–0·63;

	Interferon beta-1a (n=107)	Alemtuzumab 12 mg/day (n=107)	Alemtuzumab 24 mg/day (n=108)	Alemtuzumab pooled (n=215)
Patients (%)	66 (62%)	66 (62%)	67 (62%)	133 (62%)
Patients with an event in 2 years of treatment	11	26	34	60
2-year Kaplan-Meier estimate of event (95% CI)	18·5% (10·7–31·1)	41·2% (30·1–54·5)	51·3% (40·0–63·8)	46·3% (38·1–55·3)
Patients with an event in 3 years of treatment	15	28	38	66
3-year Kaplan-Meier estimate of event (95% CI)	27·2% (17·2–41·4)	45·1% (33·6–58·4)	58·0% (46·3–70·1)	51·6% (43·2–60·7)
Hazard ratio (95% CI); p	..	2·14 (1·18–3·90); 0·01	3·123 (1·77–5·51); 0·0001	2·614 (1·54–4·43); 0·0004

Hazard ratios and p values are for pairwise comparisons between alemtuzumab and interferon beta-1a over 3 years.

Table 3: **Overall treatment effect for sustained reduction in disability**

p=0·0028). These changes represent a net mean advantage of 0·77 EDSS points (0·48–1·06; p<0·0001) for patients treated with alemtuzumab (web-appendix pp 15–17). Subset analyses of mean change from baseline EDSS provided evidence that a mean improvement in disability for the pooled group of patients treated with alemtuzumab occurred consistently across demographic, geographic, baseline disease characteristics, and treatment-cycle subsets (webappendix pp 15–17). Patients with MRI T1 brain volume less than 317·4 mL benefited least, with a mean improvement from baseline EDSS at month 36 of 0·39 points (95% CI –0·06 to 0·84), compared with 1·05 points (0·67–1·43) in those with MRI T1 brain volume greater than 317·4 mL (webappendix pp 15–17).

A detailed report of adverse events in patients treated with alemtuzumab was published previously.[2] Briefly, adverse events in the alemtuzumab group compared with the interferon beta-1a group included autoimmunity (thyroid 49 [23%] *vs* three [3%]), immune thrombocytopenia (six [3%] *vs* one [1%]), and infections (142 [66%] *vs* 50 [47%]). Infections were predominantly mild to moderate in severity, and none were fatal, with nine (4%) patients treated with alemtuzumab experiencing a serious infection compared with two (2%) patients treated with interferon beta-1a. Thyroid-related autoimmune adverse events were mostly mild to moderate in severity, with three (1%) of the patients in the alemtuzumab group experiencing a serious thyroid-related event. Five of the six immune thrombocytopenia cases in the alemtuzumab group were rated as serious, including one fatality. Most patients treated with alemtuzumab experienced infusion-associated reactions (213, 99%), with three (1%) patients experiencing a serious infusion-associated reaction.

Efficacy of alemtuzumab was greater than interferon beta-1a in all demographic and disease-related subgroups on all endpoints, although comparisons did not always reach traditional levels of significance (multiplicity-adjusted p value <0·0025). Even in the small number of outcomes and subgroups where a statistically significant (nominal p value <0·05) interaction was found (geographical region for CDA and relapse rate and MRI-T1 brain volume for change in EDSS. The interaction was quantitative rather than qualitative in nature, with all levels of the subgroup showing benefit for alemtuzumab. No subgroup of patients consistently responded better than others to alemtuzumab. For example, although alemtuzumab seemed to be more effective in younger people (<31 years of age) for most outcome measures, and particularly with SRD and mean EDSS (figure 4, webappendix pp 1–2), there was no effect of age on relapse rate (figure 2, webappendix pp 6–8). Similarly, patients without cerebral atrophy (MRI-T1 brain volume ≥317·4 mL) responded more favourably to alemtuzumab in terms of SAD (figure 1, webappendix pp 3–5) and mean EDSS (webappendix pp 1–2) than did those without atrophy, but brain volume did not affect the efficacy of alemtuzumab as measured by other endpoints. The largest treatment effect differences were seen between the USA and Europe geographic regions for relapse rate and CDA (figures 2 and 3, webappendix pp 6–11); however, these differences are not apparent with the other endpoints. Where there were differences in data stratified by MRI-T2 lesion volume (<9·96 mL), alemtuzumab seemed more efficacious in those with greater lesion volume (webappendix pp 3–17).

Discussion

Alemtuzumab was more effective at halting clinical disease activity than interferon beta-1a in all subgroups of patients with early, active RRMS in a phase 2 trial. The selection criteria for the CAMMS223 trial identified patients who were within the window of opportunity for immunotherapy for RRMS, where modulation of the immune response is able to alter the natural history of disability accumulation. In patients with established cerebral atrophy or a high lesion burden measured by MRI, there was a clear beneficial treatment effect of alemtuzumab over interferon beta-1a on relapse rate and risk of accumulating disability. Ongoing phase 3 trials of alemtuzumab—CARE-MS I (ClinicalTrials.gov number NCT00530348) and CARE-MS II (NCT00548405)—are exploring the efficacy of alemtuzumab in cohorts with wider inclusion criteria, including patients who have previously received disease-modifying therapies.

The recent development of therapies for multiple sclerosis that seem to be more effective than interferons and glatiramer acetate has led to the development of new,

exploratory outcome measures. Havrdova and colleagues[9] did a post-hoc analysis of the number of patients free of both relapse and 24-week disability accumulation in the pivotal AFFIRM study of natalizumab versus placebo (panel). The proportion of patients with freedom from clinical disease activity for 2 years was 41% in the placebo group and 66% in the natalizumab group. Acknowledging differences in the trial inclusion criteria and difficulties comparing outcomes across studies, the sustained treatment benefits of alemtuzumab as measured by freedom from 3-month CDA compare favourably with natalizumab at 2 years (80% of patients free of CDA) and 3 years (68% of patients free of CDA). This is notable considering that at year 3, about 80% of patients treated with alemtuzumab had received no treatment for 2 years, whereas patients treated with natalizumab continued to receive treatment each month. The more complete metric of freedom from disease activity, which combines clinical and MRI data, also promoted by Havrdova and colleagues,[9] could not be calculated in this study because gadolinium-enhanced MRI scans were not done routinely.

An effect not previously described in phase 2 or 3 trials in multiple sclerosis, until CAMMS223, is an improvement in disability after treatment. We previously measured this as a change in group mean and median EDSS. These statistics can be criticised as inappropriate to derive from an ordinal scale, and could be influenced by unsustained fluctuations in EDSS. Here we present a relatively new outcome measure for clinical trials in multiple sclerosis—sustained reduction in disability—as a method of capturing clinically meaningful improvements in EDSS, at the level of the individual patient. This method excludes those with little or no disability at entry, restricting analysis to those with a baseline EDSS score of 2·0 or greater. By this method, patients treated with alemtuzumab were almost twice as likely to achieve SRD compared with patients treated with interferon beta-1a. In the AFFIRM study, 21% of patients treated with natalizumab experienced a 24-week SRD at year 2,[8] whereas 46% of patients treated with alemtuzumab achieved SRD by 2 years.

The mechanisms underlying disability reduction after alemtuzumab are not clear and the subgroup analyses presented here do not add to our understanding. The rationale behind the selection criteria of the CAMMS223 trial was to identify patients with early multiple sclerosis, in whom the capacity for repair and plasticity were presumed to be greatest. We have argued elsewhere that the improvement in EDSS may not be simply attributable to greater suppression of disease activity by alemtuzumab than by interferon beta-1a; following our finding that peripheral lymphocytes reconstituted after alemtuzumab secrete neurotrophins in response to myelin antigen, we have speculated that alemtuzumab might be inducing protective autoimmunity and supporting endogenous brain repair.[10] We are testing this hypothesis further with imaging techniques designed to identify tissue repair.

***Panel:* Research in context**

Systematic review

We report the results of subset analyses of the CAMMS223 study, the efficacy and safety outcomes of which were reported in *The New England Journal of Medicine*.[2] An electronic literature search using the keywords "multiple sclerosis", "disability", "relapse", "disease free", "improvement", "subset", and "cohort", later narrowed to "disease-modifying therapy", "clinical trials", and recently published (2000 and later) was done to identify reports of clinical trials that investigated a reduction in disability or freedom from clinical disease activity. The AFFIRM[9] study was identified as the most relevant comparison, being the only other clinical trial in which freedom from clinical disease activity has been analysed. We also identified the presentation by Munschauer and colleagues[8] as relevant to our analysis of sustained improvement in disability, also from the AFFIRM trial.

Interpretation

Our study provides evidence that alemtuzumab is consistently more effective than interferon beta-1a across different subgroups. Additionally, we describe a new way in which to quantify disability improvement in patients with multiple sclerosis. The CAMMS223 trial was the first trial in which the investigational product led to an improvement in disability in a substantial proportion of patients. In our original analysis, we described this in terms of a reduction in the mean expanded disability status scale (EDSS) score; however, this has been criticised as not being appropriate to average ordinal data, and it might be affected by non-sustained fluctuations in disability. We propose a new outcome measure—sustained reduction in disability—as a more appropriate statistic, which can be treated as a cardinal scale, and captures an improvement in disability of sufficient magnitude and persistence to qualify as a meaningful change.

There are two important limitations to this study. First, it was a phase 2 study that restricted the sample of patients to an early, active RRMS population, with low disability. This necessarily reduces the generalisability of our findings. Second, the study was not powered to identify subgroup differences. The efficacy and safety of alemtuzumab is being assessed in a greater number of patients with a wider range of disease characteristics in phase 3 trials.

We conclude that alemtuzumab is more effective than interferon beta-1a, both in suppressing relapses and preventing the accumulation of disability, in all subgroups of patients with early, active RRMS within a phase 2 trial. Furthermore, alemtuzumab treatment leads to a sustained improvement in disability over three years in about half of patients with a baseline EDSS score greater than or equal to 2. Risk minimisation procedures to identify infrequent but serious adverse events, such as immune thrombocytopenia, should be considered mandatory for the safe future use of alemtuzumab.

Contributors

AJC, EF, AV, SKG, VB, KWS, AD-DB, DRW, DHM, SM, and DASC provided medical oversight of study patient care and/or study conduct. They and SLL and JP participated in designing the analysis. SLL and JP did the programming and data analysis. AJC and MSS wrote the paper, and all authors reviewed and provided input on the final version of the article.

Conflicts of interest

AJC has received consulting fees, lecture fees, and institutional grant support from Genzyme, Merck Serono, and UCB-Celltech. EF has received consultancy fees, honoraria, travel expenses, and research support from Bayer, Biogen Idec, EMD Serono, Genzyme, Opexa Therapeutics, Pfizer, Teva Neuroscience, and Eli Lilly. AD-DB has received fees for board membership and lectures for Genzyme, Teva Neuroscience, Serono, Pfizer, Biogen, and Novartis. DW has received consulting fees, lecture fees, and institutional research support from Genzyme, EMD Serono, Pfizer, Biogen Idec, Teva Neuroscience, Elan, XenoPort, UCB, Facet, Novartis, Ono Pharmaceuticals, Synthon BV, Eli Lilly, Avanir, Acorda, Opexa Therapeutics, Cephalon, GlaxoSmithKline, Forest, Allergan, Sepracor, National Institute of Health, and the National MS Society. DM, SL, SM, JP, and MSS are employees of Genzyme. DASC has received consulting fees, lecture fees, and grant support from Genzyme, and lecture fees from Bayer Schering Pharma on behalf of himself and the University of Cambridge.

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