Alemtuzumab more effective than interferon β-1a at 5-year follow-up of CAMMS223 Clinical Trial

A.J. Coles, MD, PhD
E. Fox, MD, PhD
A. Vladic, MD
S.K. Gazda, MD
V. Brinar, MD, PhD
K.W. Selmaj, MD, PhD
A. Skoromets, MD
I. Stolyarov, MD, PhD
A. Bass, MD
H. Sullivan, MD
D.H. Margolin, MD, PhD
S.L. Lake, ScD
S. Moran, MD, MSCE
J. Palmer, MS
M.S. Smith, PhD
D.A.S. Compston, MD, PhD

Correspondence & reprint requests to Dr. Coles: ajc1020@medschl.cam.ac.uk

ABSTRACT

Objective: To report the long-term safety and efficacy results from CAMMS223 comparing alemtuzumab with interferon β-1a in early, active relapsing-remitting multiple sclerosis (RRMS). What are the long-term effects of alemtuzumab treatment, received 36 to 48 months previously, on relapse and disability in early, active RRMS? This study provides evidence of the effectiveness of alemtuzumab in reducing the relapse rate and accumulation of disability compared with interferon β-1a (IFNβ-1a) through extended follow-up (up to 60 months from baseline).

Methods: Of 334 patients originally randomized, 198 participated in the extension phase (151 [68%] alemtuzumab and 47 [42%] IFNβ-1a). Disability, relapses, and safety were assessed as in the original study period. Efficacy outcomes were analyzed from baseline of the original trial period to 60 months. Safety data extended beyond 60 months.

Results: Over 5 years, alemtuzumab lowered the risk of sustained accumulation of disability by 72% and the rate of relapse by 69% compared with IFNβ-1a (both $p < 0.0001$). The annualized relapse rate from baseline to month 60 was 0.11 for alemtuzumab and 0.35 for IFNβ-1a. Complete safety follow-up reflected 988 and 376 person-years for alemtuzumab and IFNβ-1a patients, respectively. Serious infections were seen in 7% of alemtuzumab patients and 3% of IFNβ-1a patients, and thyroid disorders were seen in 30% of alemtuzumab patients vs 4% of IFNβ-1a patients. Immune thrombocytopenia occurred in 3% of alemtuzumab patients and 0.9% of IFNβ-1a patients during the initial study period; no additional events were reported during the extension phase. One alemtuzumab patient developed Goodpasture disease 39 months after the second annual cycle of alemtuzumab.

Conclusions: Through extended follow-up, alemtuzumab remained significantly more efficacious than IFNβ-1a, with a safety profile consistent with previous reports.

Classification of Evidence: This study provides Class III evidence that alemtuzumab is more effective than interferon β-1a in reducing relapses and disability in patients with RRMS in a long-term follow-up of a rater-blinded, randomized clinical trial with 59.5% of patients participating in the extended follow-up period. *Neurology*® 2012;78:1069–1078

GLOSSARY

AE = adverse event; **ARR** = annualized relapse rate; **DMT** = disease-modifying therapy; **EDSS** = Expanded Disability Status Scale; **GBM** = glomerular basement membrane; **IFNβ-1a** = interferon β-1a; **ITP** = immune thrombocytopenia; **LLN** = lower limit of normal; **MS** = multiple sclerosis; **RRMS** = relapsing-remitting multiple sclerosis; **SAD** = sustained accumulation of disability; **SAE** = serious adverse event; **SC** = subcutaneous.

Alemtuzumab is an anti-CD52 humanized monoclonal antibody that alters the circulating lymphocyte pool.[1–3] It demonstrated significant efficacy as a treatment for relapsing-remitting multiple sclerosis (RRMS) in preliminary studies[4,5] and in a phase 2 clinical trial of more than 300 participants followed for up to 36 months (CAMMS223), reducing the rate of relapse and

Supplemental data at www.neurology.org

Supplemental Data

From the Department of Neurosciences (A.J.C., D.A.S.C.), University of Cambridge, Addenbrooke's Hospital, Cambridge UK; Central Texas Neurology Consultants (E.F.), Round Rock, TX; 3General Hospital 'Sv Duh' (A.V.), Zagreb, Croatia; INTEGRA Clinical Research (S.K.G.), San Antonio, TX; Zagreb Medical School and University Hospital Center (V.B.), Zagreb, Croatia; Medical University of Lodz (K.W.S.), Lodz, Poland; I.P. Pavlov's State Medical University (A.S.), St. Petersburg, Russia; Institute of the Human Brain of Russian Academy of Sciences (I.S.), St. Petersburg, Russia; Neurology Center of San Antonio (A.B.), San Antonio, TX; Hauenstein Center (H.S.), St. Mary's Health Care, Grand Rapids, MI; Genzyme Corporation (D.H.M., S.L.L., S.M., J.P.), Cambridge, MA; and ReSearch Pharmaceutical Services, Inc. (M.S.S.) Fort Washington, PA.

Study funding: Supported by Genzyme Corporation and Bayer Healthcare Pharmaceuticals.

Disclosure: Author disclosures are provided at the end of the article.

the risk of sustained accumulation of disability by more than 70% compared with subcutaneous (SC) interferon β-1a (IFNβ-1a). Furthermore, the mean disability of alemtuzumab patients improved at month 36 in contrast with mean disability worsening in the IFNβ-1a group.[6] In post hoc analysis of the improvement in disability, a sustained reduction in disability was more than twice as likely to occur among alemtuzumab-treated patients than among IFNβ-1a–treated patients.[7] Treatment effects were evident 2 years after the last treatment on all efficacy measures for the subset of patients who only received 2 cycles of alemtuzumab.[7] Notable adverse events (AEs) associated with alemtuzumab included infusion-associated reactions, infections of predominantly mild to moderate severity, and secondary autoimmunity (primarily thyroid disorders and less commonly immune thrombocytopenia).[6]

Patients in CAMMS223 were invited to participate in an extension of CAMMS223 to explore 1) the continued durability of the treatment effect of alemtuzumab and 2) the long-term safety profile.

METHODS

The enrollment criteria and study design for the original 36-month study period of CAMMS223 have been published previously[6] and are summarized here.

Patients and procedures for CAMMS223 original 36-month study. From December 2002 to July 2004, 334 people with treatment-naive RRMS were enrolled at sites in 5 countries. Enrollment criteria were Expanded Disability Status Scale (EDSS)[8] scores ≤3.0, disease duration ≤3 years, at least 2 relapses in the previous 2 years, and the presence of at least one gadolinium-enhancing lesion on a screening MRI scan. Patients were randomly assigned 1:1:1 to either IFNβ-1a (44 μg/day 3 times weekly) or up to 3 annual IV cycles of alemtuzumab (3- to 5-day cycles) at a dose of 12 or 24 mg/day. Patients were not blinded to treatment group but were assessed by blinded raters. The planned study period for each patient was 36 months. The last patient's final study visit for the original study period was September 2007. In September 2005, alemtuzumab therapy was suspended after immune thrombocytopenia (ITP) developed in 3 patients with one fatality. During the dosing suspension, all safety and efficacy assessments proceeded as planned, and patients who were receiving IFNβ-1a continued to receive that drug. A program to ensure prompt identification and management of ITP was implemented, and the study duration was extended. The dosing suspension was lifted in April 2008.

Procedures for extension period of CAMMS223. The extension phase started in August 2006. All CAMMS223 patients were encouraged to participate, including those who had previously withdrawn. The use of disease-modifying therapies (DMTs), including IFNβ-1a, was permitted, although these treatments were not provided by the study. After the lifting of the dose suspension in 2008, the sponsor introduced the option of redosing alemtuzumab patients, at least 12 months after their last alemtuzumab treatment. Retreatment alemtuzumab cycles consisted of 3 consecutive days of 12 mg/day, with methylprednisolone premedication. Each patient was followed for 4 years or until CAMMS223 ended in January 2010, when a new extension study opened for patients participating in CAMMS223 and 2 phase 3 clinical trials.

Outcome assessments. A blinded rater evaluated disability quarterly and before a retreatment cycle using the EDSS and sought objective signs required to confirm suspected relapses as needed. Surveillance for thyroid abnormalities and ITP continued during the extension. Monthly serum creatinine and urinalysis testing for all alemtuzumab patients began after one patient in this study developed anti-glomerular basement membrane (GBM) disease (Goodpasture disease). Lymphocyte phenotyping occurred quarterly and at 1 month after each alemtuzumab cycle during the original 36-month study period. During the extension phase, lymphocyte phenotyping occurred annually for all alemtuzumab patients and for patients retreated with alemtuzumab at alemtuzumab retreatment, 1 month after retreatment, and semiannually.

Statistical analysis. The analyzed intention-to-treat dataset included patients with continuous follow-up and those who discontinued during the original study period but re-enrolled in the extension. Post hoc analyses were performed through 60 months after randomization. Supplemental efficacy analyses were conducted using all available data (complete follow-up). Safety results used all available data through the closing of CAMMS223.

Sustained accumulation of disability (SAD) was defined as a ≥1.0 point increase in EDSS score if the baseline EDSS score was >0 (or a ≥1.5 point increase if the baseline EDSS score was 0) sustained for a 6-month period. Time to SAD was assessed by a proportional hazards model with covariates for treatment group, country, and baseline EDSS score. Annualized relapse rate (ARR) was estimated with Poisson regression with treatment group as the only covariate. Treatment effects for relapse rate were compared using an Andersen-Gill model with robust variance estimation and treatment group, country, and baseline EDSS score as covariates. Treatment group comparisons for median change from baseline in EDSS scores were made using the Wilcoxon-Mann-Whitney test. A proportional odds model was used to assess improvement, stability, or worsening in EDSS scores from baseline. Proportions of patients with and without SAD and relapse were estimated with the Kaplan-Meier method. All p values are 2-sided and were not adjusted for multiple hypothesis testing.

Sensitivity analyses were conducted, censoring patients at the time when they received any nonstudy DMT during the first 36 months of the trial and any DMT, including IFNβ-1a or alemtuzumab retreatment, during the extension phase.

Because of incomplete follow-up and the possibility of informative dropout biasing the estimated treatment effects,[9] sensitivity analyses were conducted using inverse probability weighting methodology.[10] The probability of dropping out of the study was estimated for each patient by fitting a logistic regression model with number of relapses and occurrence of a SAD event as explanatory variables and a variable indicating whether the patient dropped out after 36 months as the outcome. Patients who initially withdrew after 36 months and then re-enrolled during the extension period were not included. Time to SAD was then analyzed using a proportional hazards regression model with each

patient weighted by the inverse of the estimated probability that they would drop out.

The median time to lymphocyte recovery for alemtuzumab-treated patients was estimated using the Kaplan-Meier method from the time of the last alemtuzumab treatment. Patients were censored at the time they were retreated with alemtuzumab or received an alternative DMT.

AEs were summarized using all evaluable data from treated patients' baseline through complete follow-up ending in January 2010. The event rate per 100 patient-years for AEs was calculated and accompanied by an exact Poisson confidence interval.

Classification of evidence. This study provides Class III evidence for the 5-year efficacy (disability and relapse rate) of alemtuzumab (12 or 24 mg/day in 2 or 3 brief annual cycles) in patients with early, active RRMS compared with 44 μg 3 times weekly IFNβ-1a; it summarizes the safety profile of alemtuzumab over 988 person-years of follow-up. Risk for SAD was 72% lower, and relapse rate was 69% lower through 5 years after alemtuzumab compared with those for IFNβ-1a (both p values <0.0001). ARR from baseline to month 60 was 0.11 for alemtuzumab and 0.35 for IFNβ-1a. The safety profile was consistent with previous reports.

Standard protocol approvals, registrations, and patient consents. CAMMS223 is registered at ClinicalTrials.gov number NCT00050778. All procedures were approved by local institutional ethics review boards of the participating sites. Patients provided written informed consent.

RESULTS

Patients. Patient disposition and DMT use during extended follow-up are presented in figure 1 and table e-1 on the *Neurology*® Web site at www.neurology.org. More alemtuzumab patients participated in the extension than IFNβ-1a patients. The median duration of follow-up after the first treatment was 57.3 months; the longest follow-up was 80.6 months. Safety follow-up reflected 988 person-years for alemtuzumab patients and 376 person-years for IFNβ-1a patients. Baseline demographic and disease characteristics were similar between patients who participated and who did not participate in the extension and were balanced across treatment groups for those who participated in the extension (table e-2). Alemtuzumab patients who did or did not participate in the extension period did not differ in ARR, but those who participated in the extension had a lower rate of SAD through the initial 36 months of the study than those who did not participate in the extension. IFNβ-1a patients who participated in the extension had a lower ARR and a lower rate of SAD through month 36 than those who chose not to continue in the study (table e-2). Patients receiving additional DMTs did not differ on baseline demographic and disease characteristics from those who did not receive additional DMTs.

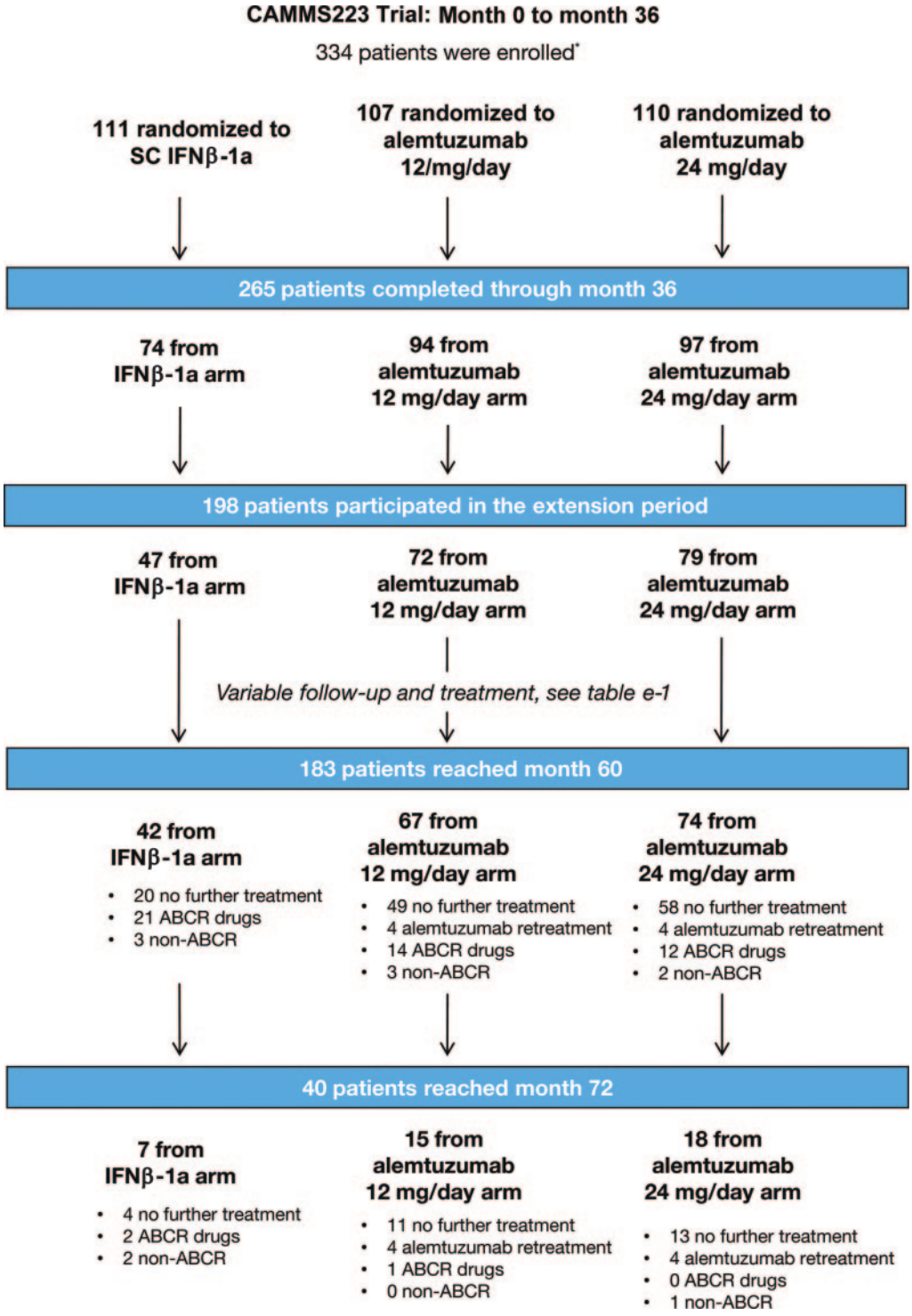
Most alemtuzumab patients received no further therapy in the extension study. Between 36 and 60 months, 9 alemtuzumab patients were retreated with alemtuzumab, of whom one had no further EDSS assessments. Forty-one alemtuzumab patients received a retreatment cycle after month 60. Each patient had just one alemtuzumab retreatment cycle. As in the original CAMMS223 study phase, the 2 dose groups of alemtuzumab did not significantly differ on efficacy or safety outcomes so a pooled dose analysis is included.

Disability. The risk of SAD was lower for alemtuzumab patients compared with that for IFNβ-1a patients at month 60 (table 1, figure 2A). A similar reduction in the risk of SAD was seen in those patients who received only 2 cycles of alemtuzumab during the original study period, at months 0 and 12 (table e-3). The mean disability of alemtuzumab patients at month 60 was improved compared with baseline, whereas it had worsened in IFNβ-1a patients, resulting in a net advantage of 0.76 EDSS point for alemtuzumab patients (table 1, figure 2B). This disability improvement was achieved by month 36; the change in mean or median disability from month 36 to 60 did not differ between alemtuzumab and IFNβ-1a patients, with both groups experiencing a small mean worsening over the longer-term follow-up period (table 1). Results through complete follow-up (table e-4) and after sensitivity analyses, censoring for alemtuzumab retreatment and DMT use, were similar (table e-5).

Relapse. The relapse rate of alemtuzumab patients was lower than that of IFNβ-1a patients from baseline to 60 months of follow-up and was lower between months 36 and 60 (table 1, figure 2, C and D). A similar ARR reduction was seen for alemtuzumab patients who received only 2 cycles during the original study period compared with IFNβ-1a patients (table e-3). The estimated percentage of relapse-free patients at month 60 was significantly higher after alemtuzumab than after IFNβ-1a (table 1). Results through complete follow-up (tables e-4 and e-5) and after sensitivity analyses censoring at the time of additional or alternative multiple sclerosis (MS) treatment were similar at month 60 with one exception. Specifically, the ARRs from month 36 to month 60 for this sensitivity analysis were lower in both treatment groups and not significantly different between treatment groups compared with the ARRs during this time period for the overall (nonsensitivity) analysis (table e-5).

Sensitivity analysis for informative dropout. IFNβ-1a–treated patients were less likely to participate in the extension. An analysis for informative dropout indicated that a SAD event was marginally related to not participating in the extension period ($p < 0.1$). The total number of relapses was not significantly related. The risk of SAD through complete follow-

Figure 1 Patient disposition



Number of patients at each time point includes all patients who have at least one Expanded Disability Status Scale (EDSS) assessment on or after that visit. Number of patients participating in extension includes all patients who have at least one EDSS assessment during the extension period. ABCR = Avonex, Betaseron, Copaxone, and Rebif; IFNβ-1a = interferon β-1a. *One patient who received alemtuzumab (12-mg group) was excluded from the efficacy analyses (but was included in the safety analysis) because the initial diagnosis of MS was incorrect. The patient did not participate in the extension period.

up, adjusted by the estimated probability of a patient dropping out, still yielded a significant treatment effect (67% reduced risk for the pooled alemtuzumab group vs IFNβ-1a; $p < 0.0001$).

Lymphocyte reconstitution. The estimated median time to total lymphocyte counts rising to the lower limit of normal (LLN) (1.0×10^9/L) was 9 months after the last alemtuzumab cycle. CD4 and CD8

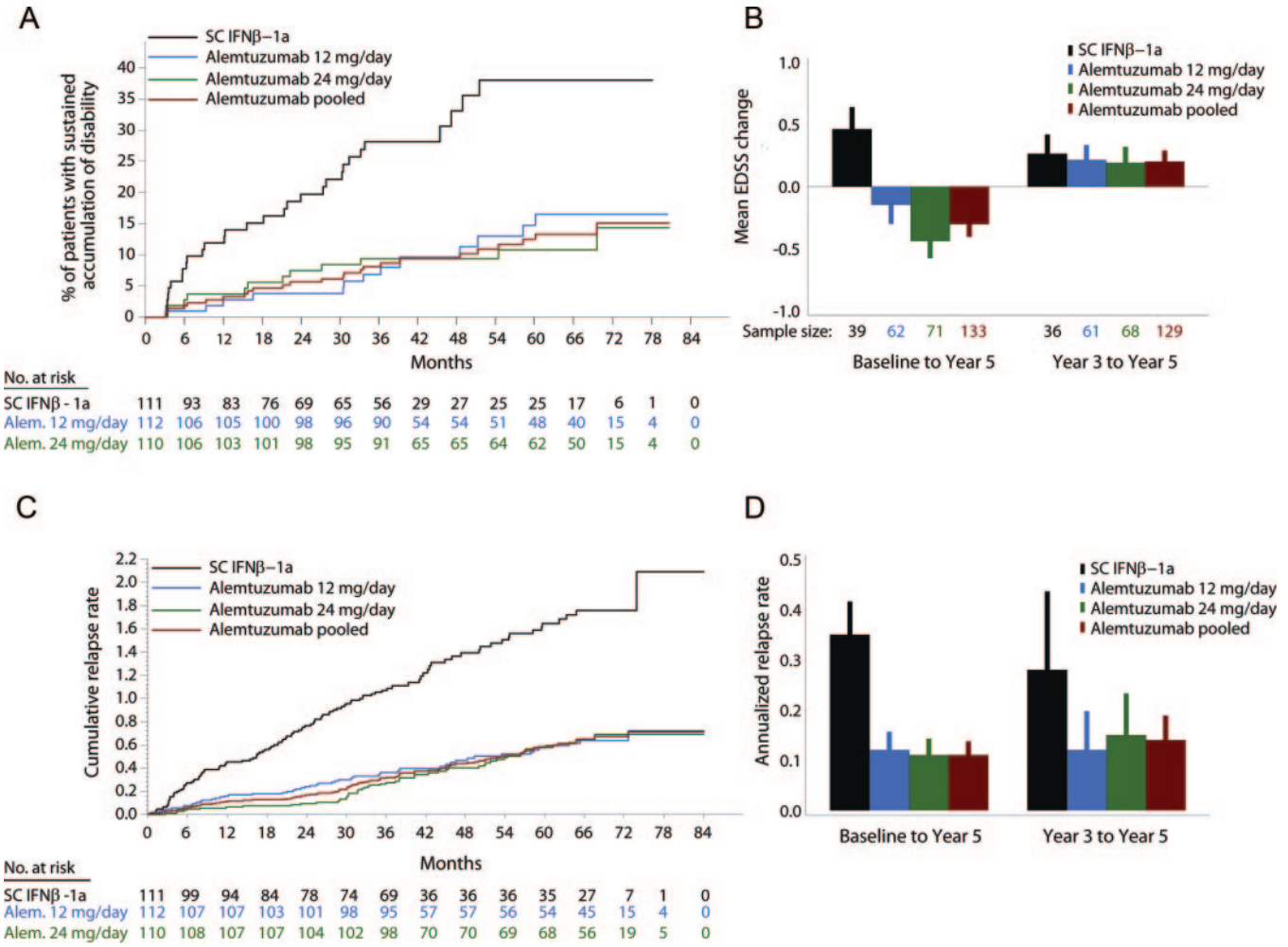
Table 1 Efficacy of alemtuzumab vs SC IFNβ-1a

Outcome and statistic	SC IFNβ-1a (n = 111)	Alemtuzumab 12 mg (n = 112)	Alemtuzumab 24 mg (n = 110)	Alemtuzumab Pooled (n = 222)
SAD from baseline to month 60				
Patients with event, n	30	13	11	24
KM estimate of no event, % (95% CI)	62 (49-73)	84 (73-90)	89 (81-94)	87 (81-91)
Hazard ratio (95% CI)		0.31 (0.16-0.60)	0.25 (0.13-0.51)	0.28 (0.16-0.48)
Treatment effect, %		69	75	72
p Value		0.0005	0.0001	<0.0001
No. needed to treat to prevent 1 SAD event (95% CI)				4.18 (2.70-9.33)
Change in EDSS score from baseline to month 60				
n	39	62	71	133
Mean change (SE)	0.46 (0.18)	−0.15 (0.15)	−0.44 (0.14)	−0.30 (0.10)
p Value		0.0056	0.0001	0.0002
Improved, n (%)	10 (25.6)	33 (53.2)	36 (50.7)	69 (51.9)
Stayed the same, n (%)	11 (28.2)	13 (21.0)	22 (31.0)	35 (26.3)
Deteriorated, n (%)	18 (46.2)	16 (25.8)	13 (18.3)	29 (21.8)
Odds ratio for improved disability (95% CI)		2.65 (1.22-5.76)	2.64 (1.22-5.71)	2.64 (1.32-5.31)
p Value		0.014	0.014	0.0063
Change in EDSS score from month 36 to month 60				
n	36	61	68	129
Mean change (SE)	0.26 (0.15)	0.21 (0.12)	0.19 (0.13)	0.20 (0.09)
p Value		0.78	0.70	0.71
Improved, n (%)	6 (16.7)	16 (26.2)	13 (19.1)	29 (22.5)
Stayed the same, n (%)	19 (52.8)	24 (39.3)	36 (52.9)	60 (46.5)
Declined, n (%)	11 (30.6)	21 (34.4)	19 (27.9)	40 (31.0)
Odds ratio for improved disability (95% CI)		1.14 (0.52-2.49)	1.15 (0.52-2.51)	1.14 (0.56-2.32)
p Value		0.74	0.73	0.71
Relapses to month 60[a]				
Patients with any event, n	51	30	22	52
Total no. of events	112	50	49	99
KM estimate of no event, % (95% CI)	41 (29-52)	68 (56-77)	77 (67-84)	72 (65-78)
No. needed to treat to prevent 1 patient from experiencing a relapse (95% CI)				3.56 (2.38-7.08)
ARR from baseline to month 60 (95% CI)[b]	0.35 (0.29-0.42)	0.12 (0.09-0.16)	0.11 (0.08-0.14)	0.11 (0.09-0.14)
Rate ratio (95% CI)[c]		0.34 (0.20-0.57)	0.29 (0.17-0.50)	0.31 (0.20-0.48)
Treatment effect, %		66	71	69
p Value		<0.0001	<0.0001	<0.0001
ARR from month 36 to month 60 (95% CI)[b]	0.28 (0.18-0.44)	0.12 (0.07-0.20)	0.15 (0.10-0.23)	0.14 (0.10-0.19)
Rate ratio (95% CI)[c]		0.44 (0.17-1.14)	0.52 (0.20-1.37)	0.48 (0.22-1.07)
Treatment effect, %		56	48	52
p Value		0.090	0.19	0.072

Abbreviations: ARR = annualized relapse rate; CI = confidence interval; EDSS = Expanded Disability Status Scale; IFNβ-1a = interferon β-1a; KM = Kaplan-Meier; SAD = sustained accumulation of disability.
[a] Assessed with the Kaplan-Meier method.
[b] Assessed with Poisson regression.
[c] Assessed with the Andersen-Gill model.

lymphocytes reconstituted gradually, reaching the LLN range an estimated median of 12 months for CD4 (LLN 0.3 × 10^9/L) and 11 months for CD8 (LLN 0.2 × 10^9/L for CD8) after the last alemtuzumab cycle. CD19 counts rose to the LLN range (0.1 × 10^9/L) quickly after each alemtuzumab cycle (median 3 months). The percentage of alemtuzumab-treated patients at month 60 with a total lympho-

Figure 2 Efficacy outcomes through month 60 and complete follow-up



(A) Kaplan-Meier estimates of time to sustained accumulation of disability through complete follow-up with the number of at-risk patients listed below. (B) The mean change from baseline of the original study period through years 5 and from year 3 to year 5 in EDSS score. (C) The cumulative relapse rate from randomization through complete follow-up. (D) The annualized relapse rate from baseline of the original study through year 5 and from year 3 to year 5. Alem. = alemtuzumab; IFNβ-1a = interferon β-1a; SC = subcutaneous.

cyte count within the normal range was 90%, for CD4 was 94%, for CD8 was 88%, and for CD19 was 96%.

Safety. The safety profile for alemtuzumab remained similar to that found during the original study period,[6] with notable AEs being infusion-associated reactions, infections, and secondary autoimmunity (table 2). AEs associated with IFNβ-1a continued to be consistent with its known safety profile, including injection reactions, flu-like symptoms, mild self-limiting abnormalities in liver transaminases, and thrombocytopenia. No additional deaths were reported in the alemtuzumab group, but one additional death due to an accident occurred in the IFNβ-1a group. The alemtuzumab-treated patient diagnosed off-study with Burkitt lymphoma, reported previously,[6] died while off-study.

Infusion-associated reactions among the 50 patients retreated with alemtuzumab during complete follow-up were qualitatively the same as those reported for the initial 3-year treatment period[6] but were reported by fewer patients (46% compared with 99% of patients at 3 years).

From the beginning of the extension phase to complete follow-up, when the majority of alemtuzumab patients were untreated, the proportion of patients with infections in a given year ranged between 10 and 27%. We note that similar proportions of patients (18–31%) had infections after IFNβ-1a in years 1–3 of the original study period (figure 3A). In contrast, after treatment during the original study period and retreatment during the extension period, the proportion of alemtuzumab patients with infections in each year after an alemtuzumab cycle was 47% (102 of 216) after cycle 1, 37% (76 of 207) after cycle 2, 43% (20 of 46) after cycle 3 in the original study period, and dropped to 22% (11 of

Table 2 Adverse events summary through complete follow-up[a]

	SC IFNβ-1a (n = 107)	Alemtuzumab		
		12 mg (n = 108)	24 mg (n = 108)	Pooled (n = 216)
Follow-up, person-years	376	480	508	988
All events				
Total no.	1,689	2,724	2,815	5,539
Events per 100 person-years, n (95% CI)	449 (428–471)	567 (546–589)	554 (534–575)	560 (546–576)
SAEs				
Patients with event, n (%)	29 (27.1)	30 (27.8)	33 (30.6)	63 (29.2)
Total no.	87	60	88	148
Events per 100 person-years, n (95% CI)	23 (19–29)	13 (10–16)	17 (14–21)	15 (13–18)
Death				
Patients with event, n (%)	1 (0.9)	1 (0.9)	2 (1.9)	3 (1.4)
Events per 100 person-years, n (95% CI)	0.3 (0.007–1.5)	0.2 (0.005–1.2)	0.4 (0.05–1.4)	0.3 (0.06–0.9)
AEs leading to withdrawal				
Patients with event, n (%)	13 (12.1)	5 (4.6)	2 (1.9)	7 (3.2)
Infusion-associated reactions				
Total events through complete follow-up	NA	922	1,035	1,957
Any event, n (%)	NA	106 (98.1)	107 (99.1)	213 (98.6)
SAEs, n (%)	NA	4 (3.7)	1 (0.9)	5 (2.3)
Infections				
Patients with any event, n (%)	54 (50.5)	77 (71.3)	79 (73.1)	156 (72.2)
Total no.	133	299	301	600
Events per 100 person-years, n (95% CI)	35.4 (29.6–41.9)	62.2 (55.4–69.8)	59.2 (52.7–66.3)	60.7 (56.0–65.8)
Patients with SAE, n (%)	3 (2.8)	6 (5.6)	9 (8.3)	15 (6.9)
Total no. of SAEs	3	7	9	16
SAEs per 100 person-years, n (95% CI)	0.8 (0.2–2.3)	1.5 (0.6–3.0)	1.8 (0.8–3.4)	1.6 (0.9–2.6)
Protocol-defined ITP[b]				
Patients with any event, n (%)	1 (0.9)	2 (1.9)	4 (3.7)	6 (2.8)
Patients with SAE, n (%)	0	1 (0.9)	4 (3.7)	5 (2.3)
Thyroid-associated events				
Patients with any event, n (%)	4 (3.7)	36 (33.3)	28 (25.9)	64 (29.6)
Total no.	6	44	39	83
Events per 100 person-year, n (95% CI)	1.6 (0.6–3.5)	9.2 (6.7–12.3)	7.7 (5.5–10.5)	8.4 (6.7–10.4)
Patients with SAE, n (%)	0 (0.0)	1 (0.9)	3 (2.8)	4 (1.9)
Total no. of SAEs	0	1	3	4
SAEs per 100 person-year (95% CI)	0	0.2 (0.005–1.2)	0.6 (0.1–1.7)	0.4 (0.1–1.0)

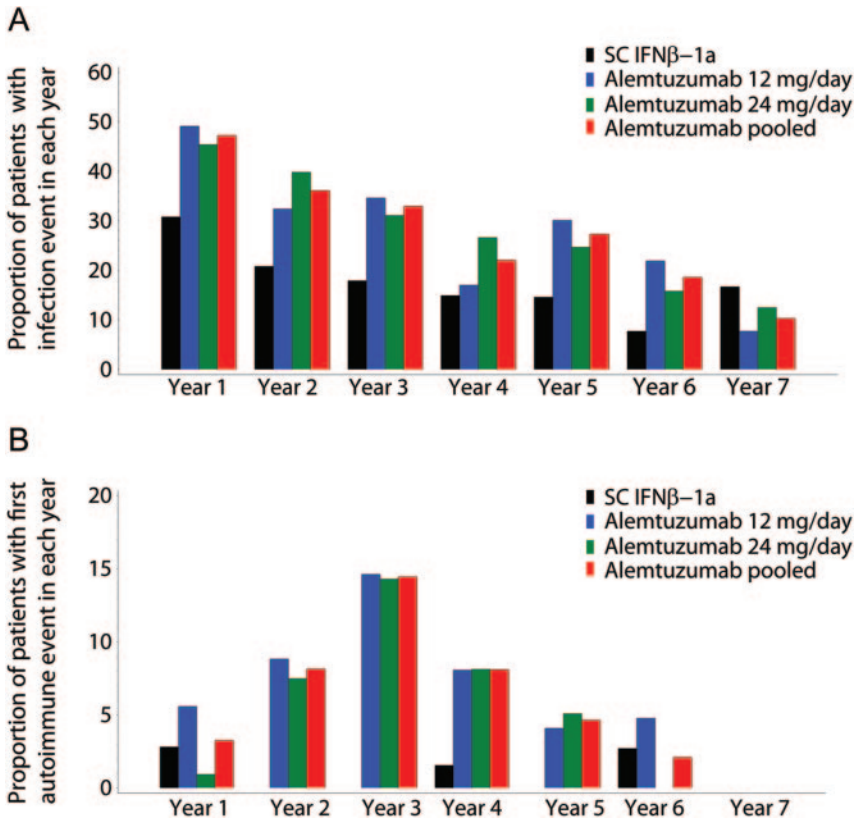
Abbreviations: AE = adverse event; CI = confidence interval; IFNβ-1a = interferon β-1a; ITP = immune thrombocytopenia; NA = not applicable; SAE = serious adverse event; SC = subcutaneous.

[a] One alemtuzumab patient was diagnosed with anti-glomerular basement membrane disease during the extension period, which was considered an SAE. Four (1.9%) alemtuzumab patients had a total of 6 malignancies (considered an SAE in 3 patients) and one (0.9%) IFNβ-1a patient had a malignancy, which was considered an SAE.

[b] The protocol definition of ITP was normal hemoglobin, normal white blood cell count (other than lymphopenia due to alemtuzumab treatment), no splenomegaly, normal peripheral smear except for a decrease in platelets without clumping, and either a confirmed platelet count ≥50,000/μL but <100,000/μL on at least 2 consecutive occasions over a period of at least 1 month or a confirmed platelet count <50,000/μL without clumping documented on at least 2 consecutive occasions over any period of time.

50) in the year after retreatment during the extension. The incidence of infections was highest during the month after an infusion. Infections through complete follow-up were predominantly mild or moderate (96%) in severity, with upper respiratory tract infections reported most frequently. No infections were life-threatening or fatal. Rates of infection were similar between patients who received 2 and 3 cycles

Figure 3 Proportion of patients with infections and first autoimmune event



(A) Proportion of patients with infections. Percentages of patients with an infection in each year of the study were based on the number of patients with evaluable safety data during that year. (B) Proportion of patients with first autoimmune event each year. Percentages of patients with first autoimmune event were based on number of patients with evaluable safety data and no prior autoimmune event other than multiple sclerosis. IFNβ-1a = interferon β-1a; SC = subcutaneous.

of alemtuzumab. Herpes infections (herpes simplex and primary and reactivation varicella zoster virus) and superficial fungal infections occurred more commonly in alemtuzumab-treated patients (17%) than in INFB-1a-treated patients (4%), but there were no disseminated infections. After year 3, annual rates of herpes simplex and superficial fungal infections were similar to rates in IFNβ-1a-treated patients in years 1–3. Only herpes zoster continued to be reported at a slightly higher frequency than that in IFNβ-1a-treated patients at <2% per year. The background rate for herpes zoster in the US population is about 3.2 per 1,000 person-years, comparable to European rates.[11]

The incidence of secondary autoimmune disease after alemtuzumab declined during the extension period (figure 3B). The most common autoimmune event was thyroid disease, seen in 30% of alemtuzumab-treated patients, with onset ranging from 6 to 61 months after the first alemtuzumab exposure, compared with 4% of IFNβ-1a–treated patients. The incidence of secondary autoimmune disease after the initial alemtuzumab treatment increased each year to a maximum in year 3 (14%) and then declined during the extension period. Patients developing thyroid autoimmunity responded to conventional therapy. No additional cases of ITP were seen in the extension period. All 5 surviving patients of the original 6 patients with ITP have maintained normal or near-normal platelet counts without additional ITP therapy or clinical sequelae for at least 41 months. One case of anti-GBM disease occurred in a 12-mg alemtuzumab-treated patient 39 months after the second annual cycle of alemtuzumab.[12] The patient was successfully treated with a course of plasmapheresis, cyclophosphamide, and corticosteroids. She has stable mild renal impairment, is not receiving treatment, and has not required dialysis or renal transplant.

During the extended follow-up, 3 additional malignancies (thyroid papillary carcinoma and 2 events of basal cell carcinoma) were reported in one 24-mg alemtuzumab patient who had left the study and entered into another investigational drug trial.

DISCUSSION We have shown that the efficacy of alemtuzumab over 3 years, as previously reported,[6] was durable for at least a further 2 years. Alemtu-

zumab continued to suppress relapses more than IFNβ-1a. The rate of SAD during the extension was low as in the earlier years. Alemtuzumab patients still had less disability at month 60 than at baseline. The positive effects of alemtuzumab on disability compared with IFNβ-1a observed in the first 36 months were maintained. This was true even for patients who had received only 2 cycles of alemtuzumab during the first year of the original study period, suggesting maintenance of efficacy 4 years after dosing, although between month 36 and 60, a slight worsening in mean disability occurred for both alemtuzumab and IFNβ-1a groups.

As with many extension studies, a limitation is the differential attrition across treatment arms. Sensitivity analyses, however, suggest that alemtuzumab's apparent long-term treatment effects are real and robust.

The safety profile reported here is consistent with our previous reports. Infection risk decreased over time from the last alemtuzumab treatment. The infection rate after retreatment during the extension was lower than rates observed during the first 36 months of the study. No discernible increased risk for malignancy is evident after alemtuzumab. As with other agents,[13,14] the rate of reported infusion-associated reactions fell with each repeated alemtuzumab cycle, perhaps suggesting increasing familiarity and skill with administration and management of alemtuzumab infusions.

The major safety concern after alemtuzumab continued to be secondary autoimmunity, most commonly autoimmune thyroid disease and less frequently ITP. Anti-GBM disease developed in one patient in this study and has been seen after alemtuzumab treatment of MS in 2 patients from other studies, who both developed end-stage renal disease requiring transplantation, as reported previously.[4,15] In this trial, early detection of anti-GBM disease led to effective treatment with minimal morbidity. To date, the secondary autoimmunity after alemtuzumab is treatable and can be reduced by early detection, achieved through education and vigilance of patient and physician and regular laboratory testing.

This extension study of the CAMMS223 trial has shown that alemtuzumab remains significantly more efficacious than IFNβ-1a over at least 5 years, with no previously unrecognized safety concerns, in patients with early, active RRMS. Risk minimization procedures to identify infrequent but serious adverse events, such as ITP and anti-GBM disease, thus far appear effective and should be an important consideration for the safe future use of alemtuzumab.

AUTHOR CONTRIBUTIONS

Dr. Coles, Dr. Fox, Dr. Vladic, Dr. Gazda, Dr. Brinar, Dr. Selmaj, Dr. Skoromets, Dr. Stolyarov, Dr. Bass, Dr. Sullivan, and Dr. Compston provided medical oversight of study patient care and/or study conduct. Dr. Coles, Dr. Compston, Dr. Margolin, Dr. Lake, Dr. Moran, and Dr. Palmer participated in designing the analyses. Dr. Lake and Dr. Palmer did the programming and data analyses. Dr. Coles and Dr. Smith wrote the paper, and all authors reviewed and provided input on the final version of the article.

DISCLOSURE

Dr. Coles serves on scientific advisory boards for Multiple Sclerosis Society of GB and NI, the International Society for Neuroimmunology, Genzyme Corporation, and Merck Serono; has received funding for travel from Merck Serono, Bayer Schering Pharma, UCB, and Genzyme Corporation; serves as the Co-Editor of *Advances in Clinical Neuroscience and Rehabilitation*; holds a patent for the use of IL-21 as a biomarker for autoimmunity after alemtuzumab; serves as a consultant for Genzyme Corporation and Merck Serono; and his department has received research support from Genzyme Corporation, UCB, and Merck Serono. Dr. Fox serves on scientific advisory boards for Biogen Idec, Teva Pharmaceutical Industries Ltd., Merck Serono, Bayer Schering Pharma, Genzyme Corporation, Opexa Therapeutics, and Novartis; has received funding for travel and speaker honoraria from Biogen Idec, Teva Pharmaceutical Industries Ltd., Merck Serono, Bayer Schering Pharma, Opexa Therapeutics, Pfizer Inc, Genzyme Corporation, and Novartis; has served as a consultant for Biogen Idec, Teva Pharmaceutical Industries Ltd., Merck Serono, Bayer Schering Pharma, Opexa Therapeutics, Genzyme Corporation, Pfizer Inc, and Novartis; serves on speakers' bureaus for Biogen Idec, Teva Pharmaceutical Industries Ltd., Merck Serono, Bayer Schering Pharma, Pfizer Inc, and Novartis; and has received research support from Ono Pharmaceutical Co. Ltd., sanofi-aventis, Eli Lilly and Company, Genzyme Corporation, and the National Multiple Sclerosis Society. Dr. Vladic, Dr. Gazda, and Dr. Brinar report no disclosures. Dr. Selmaj serves on a scientific advisory board for Genzyme Corporation; has received funding for travel and speaker honoraria from Genzyme Corporation; serves as a consultant for Genzyme Corporation, Novartis, Biogen Idec, and Roche; and serves on the speakers' bureaus for Novartis, Merck Serono, Biogen Idec, and Bayer Schering Pharma. Dr. Skoromets and Dr. Stolyarov report no disclosures. Dr. Bass serves on speakers' bureaus for and received speaker honoraria from Acorda Therapeutics Inc., Biogen Idec, Novartis, Pfizer Inc, Questcor Pharmaceuticals, Inc., Merck Serono, and Teva Pharmaceutical Industries Ltd. and receives research support from Elan Corporation, Genzyme Corporation, Novartis, and Teva Pharmaceutical Industries Ltd. Dr. Sullivan has received funding for travel and speaker honoraria from Novartis, Teva Pharmaceutical Industries Ltd., Biogen Idec, Merck Serono, and Pfizer Inc; serves as a consultant for Teva Pharmaceutical Industries Ltd.; serves on speakers' bureaus for Novartis, Teva Pharmaceutical Industries Ltd., Biogen Idec, Merck Serono, and Pfizer Inc; and receives research support from Biogen Idec. Dr. Margolin is listed as author on a patent application re: Treatment of Multiple Sclerosis—dosing regimens for alemtuzumab, an investigational therapy; is an employee of Genzyme Corporation (a sanofi-aventis company); and holds stock/stock options in Genzyme Corporation and Contingent Value Right (GCVRZ), tied to alemtuzumab approval and sales. Dr. Lake is a full-time employee of Genzyme (a sanofi company). Dr. Moran was an employee of Genzyme Corporation (a company of sanofi-aventis) and is currently an employee of Millennium Pharmaceuticals, Inc. and holds stock/stock options in Genzyme Corporation and Millennium Pharmaceuticals, Inc. Dr. Palmer is a full-time employee of Genzyme Corporation (a company of sanofi-aventis). Dr. Smith is a contract medical writer employed by Genzyme Corporation to assist with the writing of this manuscript. Prof. Compston serves as Editor of *Brain*; is author on a patent re: IL-21 as a biomarker of autoimmunity after alemtuzumab; serves as a consultant for Genzyme Corporation and Bayer Schering Pharma; and receives research support from Genzyme Corporation, Bayer Schering Pharma, and Medical Research Council UK.

Received June 11, 2011. Accepted in final form November 4, 2011.

REFERENCES

1. Cox AL, Thompson SAJ, Jones JL, et al. Lymphocyte homeostasis following therapeutic lymphocyte depletion in multiple sclerosis. Eur J Immunol 2005;35:3332–3342.
2. Jones JL, Phuah CL, Cox AL, et al. IL-21 drives secondary autoimmunity in patients with multiple sclerosis, following therapeutic lymphocyte depletion with alemtuzumab (Campath-1H). J Clin Invest 2009;119:2052–2061.
3. Thompson SAJ, Jones JL, Cox AL, Compston DAS, Coles AJ. B-cell reconstitution and BAFF after alemtuzumab. J Clin Immunol 2010;30:99–105.
4. Coles AJ, Cox A, Le Page E, et al. The window of therapeutic opportunity in multiple sclerosis: evidence from monoclonal antibody therapy. J Neurol 2006;253:98–108.
5. Fox EJ, Sullivan HC, Gazda SK, et al. A single-arm, open-label study of alemtuzumab in treatment-refractory patients with multiple sclerosis Eur J Neurol 2012;19:307–311.
6. CAMMS223 Trial Investigators. Alemtuzumab vs. interferon β-1a in early multiple sclerosis. N Engl J Med 2008;359:1786–1801.
7. Coles AJ, Fox E, Vladic A, et al. Alemtuzumab versus interferon β-1a in early relapsing-remitting multiple sclerosis: post-hoc and subset analyses of clinical efficacy outcomes. Lancet Neurol 2011;10:338–348.
8. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an Expanded Disability Status Scale (EDSS). Neurology 1983;33:1444–1452.
9. Little RJA, Rubin DB. Statistical Analysis with Missing Data. New York: John Wiley; 1987.
10. Rotnitzky A, Robins JM, Scharftstein DO. Semiparametric regression for repeated outcomes with nonignorable nonresponse. J Am Stat Assoc 1998;93:1321–1339.
11. Insinga RP, Itzler RF, Pellissier JM, et al. The incidence of herpes zoster in a United States administrative database. J Gen Intern Med 2005;20:748–753.
12. Meyer D, Coles AJ, CAMMS223 Study Group. Case report of anti-glomerular basement membrane disease following alemtuzumab treatment. Poster presented at the European Committee for Treatment and Research in Multiple Sclerosis Annual Meeting; October 13–16, 2010; Gothenburg, Sweden.
13. Vogel WH. Infusion reactions: diagnosis, assessment, and management. Clin J Oncol Nurs 2010;14:E10–E21.
14. Lenz HJ. Management and preparedness for infusion and hypersensitivity reactions. Oncologist 2007;12:601–609.
15. Clatworthy MR, Wallin EF, Jayne DR. Anti-glomerular basement membrane disease after alemtuzumab. N Engl J Med 2008;359:768–769.